Exhibit A

What is claimed is:

1. A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting essentially of:

(a) from 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(b) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and

(c) at least about 70 weight percent aqueous phase.

2. Cancel.

3. Cancel.

4. Cancel.

5. The composition of claim 1 wherein the corticosteroid comprises beclomethasone dipropionate.

6. The composition of claim 1 wherein the corticosteroid comprises budesonide.

7. The composition of claim 1 wherein the corticosteroid comprises triamcinolone acetonide.

8. The composition of claim 1 wherein the corticosteroid comprises fluticasone propionate.

9. The composition of claim 1 wherein the corticosteroid comprises flunisolide.

10. The composition of claim 1 wherein the high-HLB surfactant component comprises at least 50% by weight tocopheryl polyethylene glycol 1000 succinate.

11. Cancel.

12. A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, comprising:

(a) from 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50 percent by weight of an ethoxylated derivative of vitamin E; and

(c) at least about 70 weight percent aqueous phase.

13. The composition of claim 12 wherein the high-HLB surfactant component comprises at least 75 percent by weight of an ethoxylated derivative of vitamin E.

14. The composition of claim 12 wherein the high-HLB surfactant component comprises at least 90 percent by weight of an ethoxylated derivative of vitamin E.

15. The composition of claim 12 further comprising from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable cosolvent comprising propylene glycol, polyethylene glycol having a molecular weight between about 200 and 4000, glycerol, ethoxydiglycol, glycofurol, and ethanol, or a combination thereof.

16. The composition of claim 12 further comprising from about 0.1 to about 3 percent by weight of a low HLB surfactant having an HLB below about 8.

17. The composition of claim 12 further comprising from about 0.1 to about 3 percent by weight of an oil.

18. A method for administering a therapeutic dosage of a corticosteroid to the respiratory tract, comprising:

(a) providing a corticosteroid composition comprising:

(1) from 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form;

(2) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50 percent by weight of an ethoxylated derivative of vitamin E; and

(3) at least about 70 weight percent aqueous phase;

(b) aerosolizing the corticosteroid composition; and

(c) administering a therapeutic effective dosage of the aerosol of the corticosteroid composition by inhalation.

19. The method of claim 18 wherein the corticosteroid composition consists essentially of said corticosteroid, said aqueous phase, and said high-HLB surfactant.

20. A method for administering a therapeutic dosage of a corticosteroid to the nasal passage, comprising:

(a) providing a corticosteroid composition comprising:

(1) from about 50 μg/ml to about 10 mg/ml of a corticosteroid in dissolved form;

(2) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50 percent by weight of an ethoxylated derivative of vitamin E; and

(3) at least about 70 weight percent aqueous phase;

(b) administering a therapeutic effective dosage of the corticosteroid composition by nasal inhalation.

21. A method of preparing a diluted corticosteroid composition containing the corticosteroid in a dissolved form, comprising:

(a) dissolving a corticosteroid compound into a molten pharmaceutically acceptable high-HLB surfactant component, wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50 percent by weight of an ethoxylated derivative of vitamin E;

(b) subsequently blending the molten high-HLB surfactant component containing the dissolved corticosteroid with an aqueous phase,

wherein the aqueous phase is present in an amount of at least about 70 weight percent, and the high-HLB surfactant component is present in an amount of from about 0.1 to about 20 weight percent of the diluted corticosteroid composition.

22. The composition of claim 1 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

23. The composition of claim 1 wherein the ethoxylated derivative of vitamin E comprises at least 90% by weight of the high-HLB surfactant component.

24. The composition of claim 1 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

25. The composition of claim 1 wherein the high-HLB surfactant component comprises at least 90% by weight tocopheryl polyethylene glycol 1000 succinate.

26. The composition of claim 12 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

27. The composition of claim 12 wherein the high-HLB surfactant component comprises at least 90% by weight tocopheryl polyethylene glycol 1000 succinate.

28. The method of claim 18 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

29. The method of claim 18 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

30. The method of claim 20 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

31. The method of claim 20 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

32. The method of claim 21 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

33. The method of claim 21 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

Exhibit B

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,100	08/21/2003	Zahir Saidi	P24,800-A USA	8648

7590 10/10/2006

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EXAMINER	
SOROUSH, LAYLA	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,100	SAIDI ET AL.	
	Examiner	Art Unit	
	Layla Soroush	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2003*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-10 and 12-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,5-10 and 12-33* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1, 5-10, 12-17, 22-27 drawn to a composition, consisting essentially of: (a) from 5 ug/mL to about 5 mg/mL of a corticosteroid in dissolved form; (b) from about 0.1 to 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants present in the high HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamine E; and (c) at least about 70 wieght percent aqueous phase.

Group II, claim(s) 18-20, 28-33, drawn to a method for administering a therapeutic dosage of a corticosteroid to the respiratory tract.

Group III, claim(s) 21, drawn to a method for preparing a diluted corticosteroid containing the corticosteroid in a dissolved form.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I, II, and III lack unity because they do not share a common special technical feature. "With respect to a group of inventions claimed in an international application unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special

technical features. The expression "special technical features" is defined in PCT Rule 13.2 as meaning those features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description or drawings (if any)."(MPEP 1850 II. Determination of "Unity of Invention"). The special technical feature of Group I is composition, consisting essentially of: (a) from 5 ug/mL to about 5 mg/mL of a corticosteroid in dissolved form; (b) from about 0.1 to 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants present in the high HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and (c) at least about 70 weight percent aqueous phase, while the special feature of Group II is a method for administering a therapeutic dosage of a corticosteroid to the respiratory tract, and the special feature of Group III is a method of preparing a diluted corticosteroid composition containing the corticosteroid in a dissolved form. Prior art teaches a compound comprising a corticosteroid and a high HLB surfactant (castor oil) as stated in Group I, so the composition as claimed is not novel, and therefore, there is a lack in unity (US Pat 4299828 A (see abstract)). Additionally, the search of prior art for a composition will not necessarily lead to a method for administering a therapeutic dosage of a corticosteroid to the respiratory tract nor to a method of preparing a diluted corticosteroid composition. Because the inventions lack unity for the reasons given above and the search required for Group I is not required for Groups II or III, restriction for examination purposes as indicated is proper.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

The species are as follows:

An election of a single species of a **corticosteroid**, a single species of **a high HLB surfactant**, a single species of **a high HLB surfactant comprising an ethoxylated derivative of vitamin E**, and a single species of **a low HLB surfactant** is required.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Election

A telephone call to the attorney is not required where: 1) the restriction requirement is complex, 2) the application is being prosecuted pro se, or 3) the examiner knows from past experience that a telephone election will not be made (MPEP

812.01). Since the restriction election is considered complex, a call to the attorney for a telephone election was not made.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Soroush whose telephone number is (571)272-5008. The examiner can normally be reached on Monday through Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

Exhibit C

March 12, 2007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of Zahir Saidi and Boris Klyashchitsky
Application No. 10/019,100
Filed: August 21, 2003

Examiner: L. Soroush
Group Art Unit: 1617
Confirmation No. 8648

Aqueous Compositions Containing
Corticosteroids for Nasal and Pulmonary Delivery

(Atty. Docket No. P24800-A USA)

Filed Electronically on March 12, 2007 by Jonathan M. Dermott

---

Reply to Examiner's Requirement for
Restriction, as Set Forth in the Action, Dated October 10, 2006

Sir:

In response to the Requirement for Restriction dated October 10, 2006, Applicants elect to prosecute the claims of Group I, that is, claims 1, 5 to 10, 12 to 17, and 22 to 27. Applicants confirm their right to file divisional applications that include the non-elected claims.

The Examiner also required Applicants to elect a single species of corticosteroid. Applicants elect hereby budesonide.

The Examiner also required Applicants to elect a single species of high-HLB surfactant. Applicants elect hereby tocopheryl polyethylene glycol 1000 succinate ("TPGS").

The Examiner also required Applicants to elect a single species of high-HLB surfactant

comprising an ethoxyolated derivative of vitamin E. Applicants elect hereby tocopheryl polyethylene glycol 1000 succinate ("TPGS").

The Examiner also required Applicants to elect a single species of low-HLB surfactant. Applicants elect hereby phospholipids.

Applicants traverse the Examiner's requirement for an election of the claims of Groups I and II.

The Examiner has asserted that Groups I and II lack unity invention under PCT Rule 13.2 because they lack a shared inventive technical feature.

Applicants submit that the technical feature of the claims is the composition of claim 1, which recited in parts (a), (b), and (c) of claim 1. The methods of claims 18 to 20 require use of the composition of claim 1. Accordingly, claims 1 and 18 to 20 require the same technical features. As the claims of Groups I and II both require the same technical features, these groups do not lack unity of invention.

Should the Examiner choose to maintain the current restriction of Groups I and II, applicants submit that Rejoinder will apply. MPEP §821.04(b) states:

> Where claims directed to a product and to a process of making and/or using the product are presented in the same application, applicant may be called upon under 35 U.S.C. 121 to elect claims to either the product or a process. See MPEP § 806.05(f) and § 806.05(h). The claims to the nonelected invention will be withdrawn from further consideration under 37 CFR 1.142. See MPEP § 821 through § 821.03. However, if applicant elects a claim(s) directed to a product which is subsequently found allowable, withdrawn process claims which depend from or otherwise require all the limitations of an allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must depend from or otherwise require all the limitations of an allowable product claim for that process invention to be rejoined. Upon rejoinder of claims directed to a previously nonelected process invention, the restriction requirement between the elected product and rejoined process(es) will be withdrawn.

Applicants submit that claims 18 to 20 are methods of using the composition of claim 1 and thus Rejoinder should apply.

A favorable action is requested respectfully. It is hereby requested that the term to respond to the Office Action, dated October 10, 2006, be extended four months, from November 10, 2006 to Saturday, March 10, 2007. Payment to cover the extension fee has been submitted

electronically. The Commissioner is hereby authorized to charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 19-5425.

Respectfully submitted,

/Jonathan M. Dermott/
Jonathan M. Dermott, Ph.D.
Reg. No. 48,608

Synnestvedt & Lechner LLP
1101 Market Street, Suite 2600
Philadelphia, PA 19107-2950
Telephone - (215) 923-4466
Facsimile - (215) 923-2189

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Exhibit D

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,100	08/21/2003	Zahir Saidi	P24,800-A USA	8648

7590 05/31/2007

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EXAMINER	
SOROUSH, LAYLA	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
05/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/019,100	SAIDI ET AL.	
	Examiner	Art Unit	
	Layla Soroush	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,10,12-17 and 22-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6, 10, 12-17, and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office Action is in response to the Applicant's reply filed March 12, 2007 to the restriction requirement made on October 10, 2006.

Applicant's election of Group I claims 1, 5-10, 12-17, and 22-27 with traverse is herein acknowledged. Applicant's election of a single species of corticosteroid - budesonide, high-HLB surfactant - TPGS and high-HLB surfactant comprising ethoxylated derivative of vitamin E – TPGS, low-HLB surfactant – phospholipids, is herein acknowledged.

Applicant submits that the technical feature of the claims is the composition of claim 1. The methods of claims 18-20 require the same technical features. However, in response Examiner respectfully reiterates, "with respect to a group of inventions claimed in an international application unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" is defined in PCT Rule 13.2 as meaning those features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description or drawings (if any)."(MPEP 1850 II. Determination of "Unity of Invention"). The special technical feature of Group I is a composition, consisting essentially of: (a) from 5 ug/mL to about 5 mg/mL of a corticosteroid in dissolved form; (b) from about 0.1 to 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants present in the high HLB surfactant

component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and (c) at least about 70 weight percent aqueous phase, while the special feature of Group II is a method for administering a therapeutic dosage of a corticosteroid to the respiratory tract. The composition and the method of administering the composition are different. Additionally, the prior art teaches the composition of claim 1, and therefore, there is a lack in unity. Applicant's arguments are not found persuasive.

The requirement is still deemed proper and is therefore made **FINAL**.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000.

Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 6, 10, 12-14, and 22-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Sonne (US Pat No. 6,193,985).

The invention reads on a composition consisting essentially of: (a) from 5 ug/mL to about 5 mg/mL of a corticosteroid in dissolved form; (b) from about 0.1 to 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants present in the high HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and (c) at least about 70 weight percent aqueous phase.

The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). "A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, "the consisting essentially of" language in the claim is treated as "comprising" language and it is an applicant's burden to establish that a step practiced

in a prior art method is excluded from his claims by consisting essentially of' language." (See MPEP 2111.03)

Sonne discloses an oil in water emulsion of budesonide as nose drop or nasal spray, comprising in the oily phase 0.025 g of budesonide and 5 grams of vitamin e TPGS. The limitation of the composition having at least about 70 weight percent of aqueous phase is met by the teachings of the prior art. The limitation of claim 1, 12, 13, 14 in which the component comprises at least 50%, 75%, and 90%, respectively, by weight of an ethoxylated derivative of vitamin E is inherently taught by the prior art. The limitation of claim 1, 10, 12, 22-27 wherein the high-HLB surfactant component comprises at least 50%, 75%, 90% by weight tocopheryl polyethylene glycol 1000 succinate, is inherently taught by the prior art.

The composition "suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract" is an intended use and does not receive patentable weight in a composition claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sonne (US Pat No. 6,193,985), as discussed in claims 1, 6, 10, 12-14, and 22-27 above.

Sonne is as discussed above.

Sonne fails to exemplify the composition further containing from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable cosolvent comprising propylene glycol, polyethylene glycol having a molecular weight between about 200 and 4000, glycerol, ethoxydiglycol, glycofurol, and ethanol, or a combination thereof, 0.1 to about 3 percent by weight of phospholipids, nor 0.1 to about 3 percent by weight of an oil.

However, Sonne teaches "the formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired. Thus for example, the following co-solvents may be added: Vegetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin," meeting the limitation of claims 15 and 17.

Further, Sonne teaches "the tocopherol derivative emulsifier of the invention may be used alone or in conjunction with other known emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers. It has furthermore surprisingly been shown that various other solvents may be used in the emulsion system described above, without compromising the stability of the emulsion."

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the composition by adding the additional ingredients fo oils or alcohols such as ethanol, propylene glycol, glycerol, polyethylene

glycol or benzyl alcohol; or triacetin, or emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers. The motivation to make such an incorporation is because Sonne teaches (1) The formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired. Thus for example, the following co-solvents may be added: Vegetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin and (2) The tocopherol derivative emulsifier of the invention may be used alone or in conjunction with other known emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers. It has furthermore surprisingly been shown that various other solvents may be used in the emulsion system described above, without compromising the stability of the emulsion. Hence, the skilled artisan would have had reasonable expectation of successfully producing a composition with optimized bioadhesion, sprayability, viscosity, without compromising the stability of the emulsion.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the dose range of the Sonne composition by routine experimentation (see 2144.05 11). The motivation to optimize the dose range of the Sonne 's final formulation is because one would have had a reasonable expectation of success in achieving the safest clinical outcome.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 10, 12-17, and 22-27 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6241969 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the invention herein is directed to a composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting essentially of: (a)from about 5 ug/ml to about 5 mg/ml of a corticosteroid in dissolved form, (b)from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants is greater than about 10, and (c) at least about 70 weight percent aqueous phase whereas, the Patent is directed to an aerosolized composition for administering a therapeutic dose of a corticosteroid to respiratory tract, consisting essentially of: (a) from 5 ug/mL to about 5 mg/mL of a dissolved corticosteroid; (b) from about 0.1 to about

20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component containing one or more surfactants having an HLB of greater than 10, wherein The high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and (c) at least about 70 weight percent aqueous phase.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Soroush whose telephone number is (571)272-5008. The examiner can normally be reached on Monday through Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).

SREENI PADMANABHAN
PRIMARY EXAMINER

5/26/07

Exhibit E

Amendments to the Claims

1. (Currently amended) A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting ~~essentially~~ of :

(a) from about 5, μg/ml to about 5 mg/ml of a corticosteroid in dissolved form,

(b) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and

(c) at least about 70 weight percent aqueous phase.

2. to 4. (Canceled)

5. (Previously presented) The composition of claim 1 wherein the corticosteroid comprises beclomethasone dipropionate.

6. (Previously presented) The composition of claim 1 wherein the corticosteroid comprises budesonide.

7. (Previously presented) The composition of claim 1 wherein the corticosteroid comprises triamcinolone acetonide.

8. (Previously presented) The composition of claim 1 wherein the corticosteroid comprises fluticasone propionate.

9. (Previously presented) The composition of claim 1 wherein the corticosteroid comprises flunisolide.

10. (Previously presented) The composition of claim 1 wherein the high-HLB surfactant component comprises at least 50% by weight tocopheryl polyethylene glycol 1000 succinate.

11. (Canceled)

12. (Canceled)

13. (Currently amended) The composition of claim 15 ~~12~~ wherein the high-HLB surfactant component comprises at least 75% by weight of an ethoxylated derivative of vitamin E.

14. (Currently amended) The composition of claim 15 ~~12~~ wherein the high-HLB surfactant component comprises at least 90% by weight of an ethoxylated derivative of vitamin E.

15. (Currently amended) ~~The composition of claim 12 further comprising~~ A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting of:

(a) from about 5, µg/ml to about 5 mg/ml of a corticosteroid in dissolved form,

(b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E;

(c) at least about 70 weight percent aqueous phase; and

(d) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable cosolvent comprising propylene glycol, polyethylene glycol having a molecular weight between about 200 and 4000, glycerol, ethoxydiglycol, glycofurol, and ethanol, or a combination thereof.

16. (Original) ~~The composition of claim 12 further comprising~~ A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting of:

(a) from about 5, µg/ml to about 5 mg/ml of a corticosteroid in dissolved form,

(b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component

wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E;

(c) at least about 70 weight percent aqueous phase; and

(d) from about 0.1 to about 3 percent by weight of a low HLB surfactant having an HLB below about 8.

17. (Original) ~~The composition of claim 12 further comprising~~ A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting of:

(a) from about 5, µg/ml to about 5 mg/ml of a corticosteroid in dissolved form,

(b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E;

(c) at least about 70 weight percent aqueous phase; and

(d) from about 0.1 to about 3 percent by weight of an oil.

18. (Withdrawn) A method for administering a therapeutic dosage of a corticosteroid to the respiratory tract, comprising:

(a) providing a corticosteroid composition comprising:

(1) from about 5 µg/ml to about 5 mg/ml of a corticosteroid in dissolved form,

(2) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and

(3) at least about 70 weight percent aqueous phase;

(b) aerosolizing the corticosteroid composition; and

(c) administering a therapeutic effective dosage of the aerosol of the corticosteroid composition by inhalation.

19. (Withdrawn) The method of claim 18 wherein the corticosteroid composition consists essentially of said corticosteroid, said aqueous phase, and said high-HLB surfactant.

20. (Withdrawn) A method for administering a therapeutic dosage of a corticosteroid to the nasal passage, comprising:

(a) providing a corticosteroid composition comprising:

(1) from about 50 μg/ml to about 10 mg/ml of a corticosteroid in dissolved form,

(2) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% of an ethoxylated derivative of vitamin E; and

(3) at least about 70 weight percent aqueous phase;

(b) administering a therapeutic effective dosage of the corticosteroid composition by nasal inhalation.

21. (Withdrawn) A method of preparing a diluted corticosteroid composition containing the corticosteroid in dissolved form, comprising:

(a) dissolving a corticosteroid compound into a molten pharmaceutically acceptable high-HLB surfactant component, wherein the HLB of the surfactants present in the high-HLB surfactant component is greater than about 10, and wherein the high-HLB surfactant component comprises at least 50% of an ethoxylated derivative of vitamin E;

(b) subsequently blending the molten high-HLB surfactant component containing the dissolved corticosteroid with an aqueous phase,

wherein the aqueous phase is present in an amount of at least about 70 weight percent, and the high-HLB surfactant component is present in an amount of from about 0.1 to about 20 weight percent of the diluted corticosteroid composition.

22. (Previously presented) The composition of claim 1 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

23. (Previously presented) The composition of claim 1 wherein the ethoxylated derivative of vitamin E comprises at least 90% by weight of the high-HLB surfactant component.

24. (Previously presented) The composition of claim 1 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

25. (Previously presented) The composition of claim 1 wherein the high-HLB surfactant component comprises at least 90% by weight tocopheryl polyethylene glycol 1000 succinate.

26. (Currently amended) The composition of claim 15 ~~12~~ wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

27. (Currently amended) The composition of claim 15 ~~12~~ wherein the high-HLB surfactant component comprises at least 90% by weight tocopheryl polyethylene glycol 1000 succinate.

28. (Withdrawn) The method of claim 18 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

29. (Withdrawn) The method of claim 18 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

30. (Withdrawn) The method of claim 20 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

31. (Withdrawn) The method of claim 20 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

32. (Withdrawn) The method of claim 21 wherein the ethoxylated derivative of vitamin E

comprises at least 75% by weight of the high-HLB surfactant component.

33. (Withdrawn) The method of claim 21 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

Exhibit F

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,100	08/21/2003	Zahir Saidi	P24,800-A USA	8648

7590 02/11/2008

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EXAMINER	
SOROUSH, LAYLA	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
02/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/019,100	SAIDI ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2007*.

2a)☒ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-10 and 13-33* is/are pending in the application.

4a) Of the above claim(s) *5,7-9,18-21 and 28-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6, 10, 13-17, and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed November 29, 2007 presents remarks and arguments submitted to the office action mailed May 31, 2007 is acknowledged.

Applicant's amendments submitted November 29, 2007 is acknowledged wherein claims 1, 13-17, 26, and 27 are amended and claim 12 is cancelled.

Applicant's arguments over the 35 U.S.C. 102(e) rejection of claims 1, 6, 10, 13-14, and 22-27 over Sonne (US Pat No. 6,193,985) is not persuasive. Therefore, the rejection is maintained for reasons of record.

Applicant's arguments over the 35 U.S.C. 103(a) rejection of claims 15-17 over Sonne (US Pat No. 6,193,985), as discussed in claims 1, 6, 10, 12-14, and 22-27 is not persuasive. Therefore, the rejection is maintained for reasons of record.

Upon the approval of the Terminal Disclaimer, the ODP rejection made over U.S. Patent No. 6241969 B1 will be withdrawn. However, the rejection of record is herewith maintained for the reasons of record.

The claims corresponding to the elected subject matter are 1, 6, 10, 13-17, and 22-27 are herein acted on the merits.

The rejections are modified to address the newly added amendments:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 6, and 22-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Sonne (US Pat No. 6,193,985 – previously presented).

The invention reads on a composition consisting of: (a) from 5 ug/mL to about 5 mg/mL of a corticosteroid in dissolved form; (b) from about 0.1 to 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants present in the high HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and (c) at least about 70 weight percent aqueous phase.

Sonne discloses an oil in water emulsion of budesonide as nose drop or nasal spray, comprising in the oily phase 0.025 grams of budesonide, 5 grams of vitamin e TPGS and 12.5 grams alpha-tocopherol – (viscous oil (surfactant)) (see col 3 line 18,

col 11 Example 15). The limitation of the composition having at least about 70 weight percent of aqueous phase is met by the teachings of the water phase in the prior art (col 11 Example 15). The limitation of claim 1, 12, 13, 14 in which the component comprises at least 50%, 75%, and 90%, respectively, by weight of an ethoxylated derivative of vitamin E is inherently taught by the prior art.

The composition "suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract" is an intended use and does not receive patentable weight in a composition claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10, and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sonne (US Pat No. 6,193,985– previously presented), as discussed in claims 1, 6, and 22-27 above.

Sonne is as discussed above.

Sonne fails to teach the composition comprising a high-HLB surfactant component of at least 50%, 75%, 90% by weight tocopheryl polyethylene glycol 1000 succinate. Further, Sonne does not exemplify a composition containing from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable cosolvent comprising propylene glycol, polyethylene glycol having a molecular weight between about 200 and

4000, glycerol, ethoxydiglycol, glycofurol, and ethanol, or a combination thereof, 0.1 to about 3 percent by weight of phospholipids, nor 0.1 to about 3 percent by weight of an oil.

However, Sonne et al. teaches "Generally speaking compositions of the invention may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative solvent. The emulsion used in compositions of the invention may contain 1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w) (Col 5 lines 55-61)."

Sonne teaches "the formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired. Thus for example, the following co-solvents may be added: Vegetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin, (col 6 lines 47-59)" meeting the limitation of claims 15 and 17.

Further, Sonne teaches "the tocopherol derivative emulsifier of the invention may be used alone or in conjunction with other known emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers. It has furthermore surprisingly been shown that various other solvents may be used in the emulsion system described above, without compromising the stability of the emulsion (col 4 lines 50-56)."

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the composition by adding the additional ingredients of oils or alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin, or emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers. The motivation to make such an incorporation is because Sonne teaches (1) The formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired. Thus for example, the following co-solvents may be added: Vegetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin and (2) The tocopherol derivative emulsifier of the invention may be used alone or in conjunction with other known emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers. It has furthermore surprisingly been shown that various other solvents may be used in the emulsion system described above, without compromising the stability of the emulsion. Hence, the skilled artisan would have had reasonable expectation of successfully producing a composition with optimized bioadhesion, sprayability, viscosity, without compromising the stability of the emulsion.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the dose range of the Sonne composition by routine experimentation (see 2144.05 11). The motivation to optimize the dose range of the Sonne 's final formulation is because one would have had a reasonable expectation of success in achieving the safest clinical outcome.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 10, 12-17, and 22-27 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6241969 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the invention herein is directed to a composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting essentially of: (a)from about 5 ug/ml to about 5 mg/ml of a corticosteroid in dissolved form, (b)from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants is greater than about 10, and (c) at least about 70 weight percent aqueous

phase whereas, the Patent is directed to an aerosolized composition for administering a therapeutic dose of a corticosteroid to respiratory tract, consisting essentially of: (a) from 5 ug/mL to about 5 mg/mL of a dissolved corticosteroid; (b) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component containing one or more surfactants having an HLB of greater than 10, wherein The high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and (c) at least about 70 weight percent aqueous phase.

Response to Arguments

Applicant's arguments filed on November 29, 2007 have been considered but are not fully persuasive.

Applicant's sole argument regarding the anticipatory rejection over Sonne (US Pat No. 6,193,985) is that the claims no longer read on the prior art due to amendments reciting "consisting of" instead of "consisting essentially of" language.

However, Examiner respectfully states that the claimed invention is composition consisting of (a) the corticosteroid, (b) high HLB surfactant components which comprise ethoxylated derivates of vitamin E, (c) an aqeuous phase. The Sonne reference reads on the claimed invention because Example 15 teaches an oil in water emulsion of budesonide (corticosteroid) as nose drop or nasal spray, comprising in the oily phase 0.025 grams of budesonide (corticosteroid), 5 grams of vitamin e TPGS (surfactant) and 12.5 grams alpha-tocopherol – (viscous oil (surfactant)) (see col 3 line 18, col 11 Example 15). The limitation of the composition having at least about 70 weight percent

of aqueous phase is met by the teachings of the water phase in the prior art (col 11 Example 15).

The arguments are not persuasive and the rejection is made **FINAL**.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

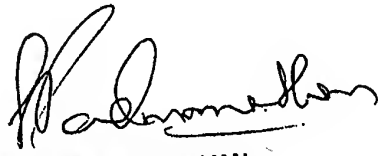
Conclusion

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Soroush whose telephone number is (571)272-5008. The examiner can normally be reached on Monday through Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

Exhibit G

US006193985B1

(12) **United States Patent**
Sonne

(10) **Patent No.: US 6,193,985 B1**
(45) **Date of Patent: *Feb. 27, 2001**

(54) **TOCOPHEROL COMPOSITIONS FOR DELIVERY OF BIOLOGICALLY ACTIVE AGENTS**

(75) Inventor: **Mette Rydahl Sonne**, Brøndby Strand (DK)

(73) Assignee: **A/S Dumex (Dumex Ltd)**, Copenhagen (DK)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/856,054**

(22) Filed: **May 14, 1997**

Related U.S. Application Data

(63) Continuation of application No. 08/441,759, filed on May 16, 1995, now abandoned.

(30) **Foreign Application Priority Data**

May 16, 1994 (GB) 9409778

(51) **Int. Cl.**[7] **A61K 9/00**; A61K 9/107

(52) **U.S. Cl.** **424/400**; 424/439; 424/484; 424/486; 514/772

(58) **Field of Search** 424/439, 450, 424/485, 486, 400, 484; 514/772

(56) **References Cited**

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WO 91/14463	10/1991	(WO) .
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Lau et al.; "Absorption of diazepam and lorazepam following intranasal administration"; *International Journal of Pharmaceutics*; 54 (1989) pp. 171–174.

Ismailos et al.; "Enhancement of cyclosporin A solubility by d–alphatocopheryl–polyethylene–glycol–1000 succinate (TPGS)"; *European Journal of Pharmaceutical Sciences*, 1 pp. 269–271(May 1994).

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Primary Examiner—Jeffrey C. Mullis
(74) *Attorney, Agent, or Firm*—Watov & Kipnes, P.C.; Allen R. Kipnes

(57) **ABSTRACT**

The present invention provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions. Such compositions are particularly suitable for transmucosal, and especially intranasal or rectal administration, or administration via the oral cavity.

30 Claims, 2 Drawing Sheets

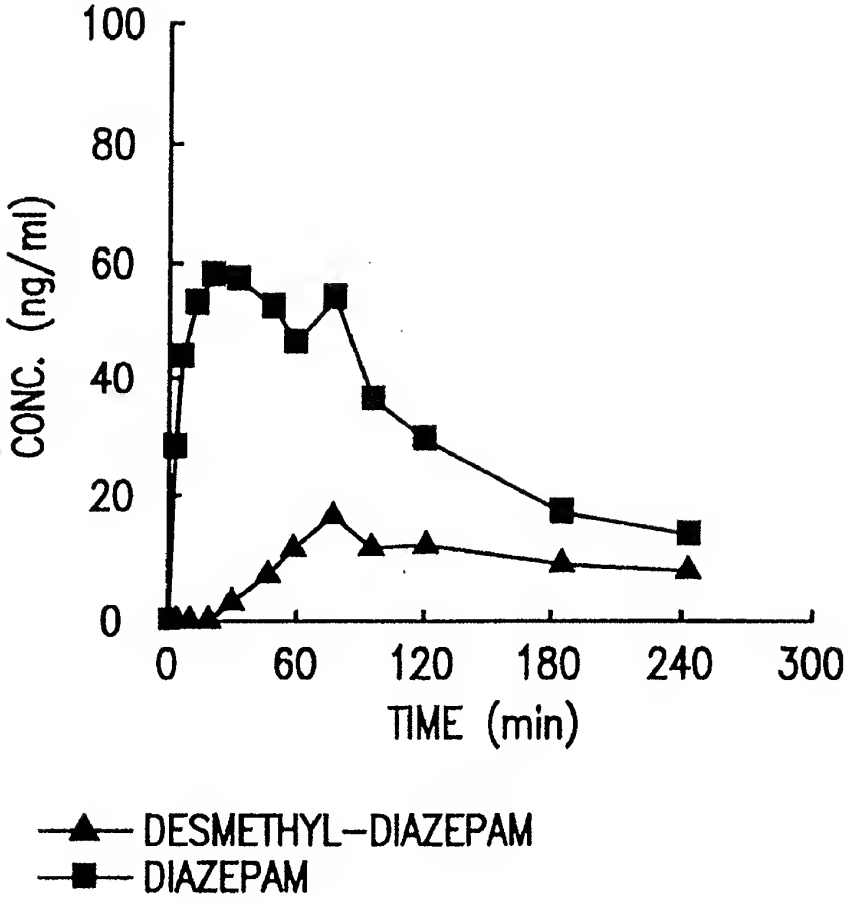
100
80
60
40
20
0
CONC. (ng/ml)
0
60
120
180
240
300
TIME (min)
DESMETHYL-DIAZEPAM
DIAZEPAM

FIG. 1

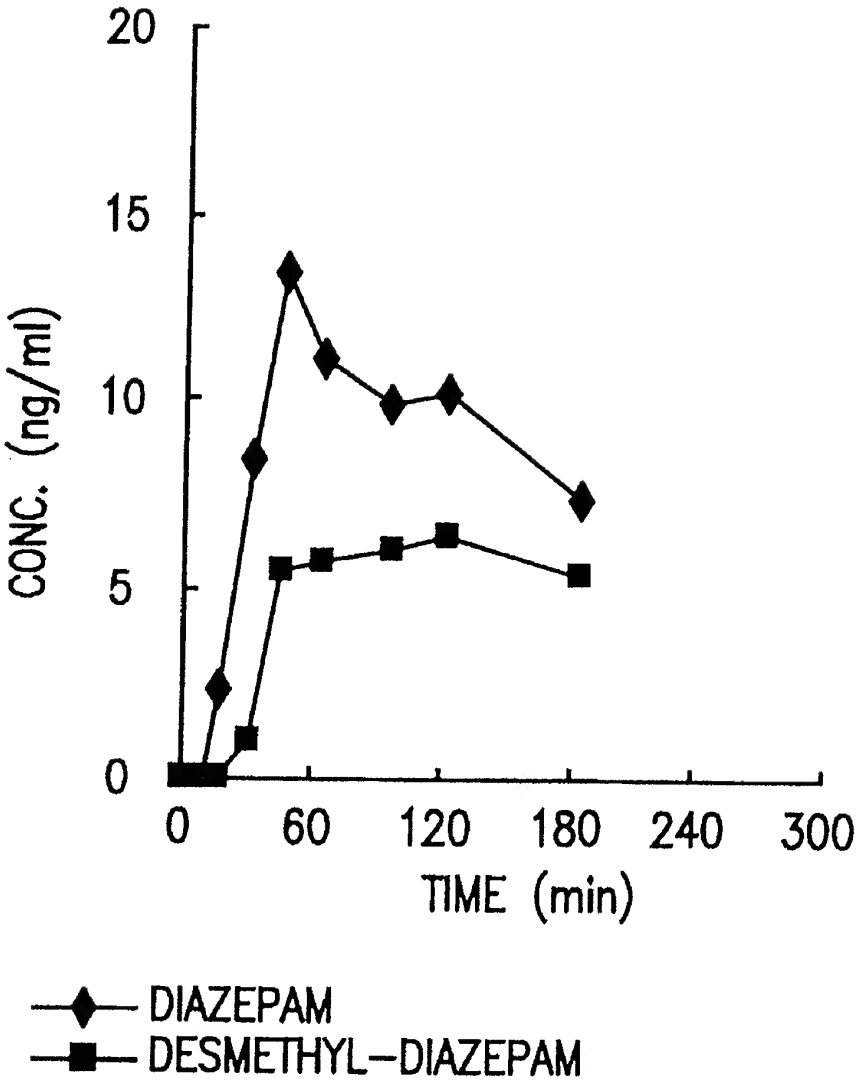
20
15
10
5
0
CONC. (ng/ml)
0
60
120
180
240
300
TIME (min)
DIAZEPAM
DESMETHYL–DIAZEPAM

FIG. 2

TOCOPHEROL COMPOSITIONS FOR DELIVERY OF BIOLOGICALLY ACTIVE AGENTS

This is a continuation application of U.S. Ser. No. 08/441,759 filed on May 16, 1995 now abandoned.

The present invention is directed to new pharmaceutical compositions for delivery of biologically active agents. More particularly, the invention concerns the use of a tocopherol or a derivative thereof to prepare compositions having low irritability suitable for administration to mucosal membranes and which may be used efficiently to administer drugs, which are substantially insoluble or only sparingly soluble in water.

For systemic action, drugs are normally administered by mouth and are then absorbed in the gastrointestinal tract. However, this mode of administration is not suitable in all circumstances, for example in the case of drugs which are metabolised to any significant degree by the liver or which are poorly absorbed. In other cases, the oral route may be impractical, for example in patients suffering from nausea or who are unconscious. Before surgery, oral administration is not advisable because of the risk of vomiting and in many cases, a more rapid effect may be required than can be achieved by the oral route.

In these circumstances the parenteral route is frequently used, most notably intravenous or intramuscular injection. However, whilst this provides a convenient way of achieving a strong and rapid systemic effect, it has a number of disadvantages including the requirement for sterile equipment and trained personnel. It is also unpleasant to the patient.

Moreover, in cases where a systemic effect is not required, local administration may be preferable, for example to avoid side effects, to reduce the dosage, or simply to facilitate the administration.

Such problems have lead in recent years to an increasing interest in developing formulations for the topical administration of drugs, and in particular for topical administration involving absorption from mucous membranes.

Topical administration has the advantage that drugs may be administered readily and simply to achieve a systemic or dermal, regional or localised effect, as required. However, topical absorption of drugs through the skin can be slow, and in many cases transmucosal routes of delivery are preferred. Since it may be performed by untrained personnel and permits therapeutic plasma levels of drugs rapidly to be achieved, intranasal administration has received particular attention in this regard.

For topical delivery, biologically active drugs are normally administered in the form of aqueous solutions. However, many biologically active compounds are substantially insoluble or only sparingly soluble in water and in such cases, organic solvents are required to dissolve these agents. The problem here is that mucosal tissues are generally very sensitive and such solvents are frequently too irritant to be of clinical use. Thus for example, Lau and Slattery [Int. J. Pharm. 1989, p. 171–74] attempted to administer the benzodiazepines diazepam and lorazepam by dissolving these compounds in a range of solvents including: triacetin, DMSO, PEG 400, Cremophor EL, Lipal-9-LA, isopropyladipate and azone dodecyle-aza-cycloheptane-2-one. Whilst many of the solvents dissolved diazepam and lorazepam in the desired concentrations, when administered to the nose they were too irritant to be of use. Thus, Cremophor EL was found to be the least irritative for mucosal tissue, but nasal absorption using this solvent is rather slow and peak concentration is low relative to that found after iv. administration.

Triglycerides such as vegetable oils are generally non-irritant, but usually these oils are too poor as solvents to be of any use.

Attempts have been made to develop various other vehicles for transmucosal delivery of drugs, such as benzodiazepines, having limited water solubility. Thus, for example WO 86/04233 of Riker discloses a pharmaceutical composition wherein the drug (eg. diazepam) is dissolved in a mixture of propellant and co-solvent eg. glycerolphosphatide. The composition requires a pressurized system and at least one halogenated hydrocarbon acrosol propellant.

In U.S. Pat. No. 4,863,720 of Burghardt, a sublingual sprayable pharmaceutical preparation is disclosed, in which the active drug can be a benzodiazepine, optionally comprising polyethylene glycol (PEG) and requiring ethanol, di- and/or triglyceride of fatty acids and a pharmaceutically acceptable propellant gas.

U.S. Pat. No. 4,950,664 of Rugby-Darby describes the nasal administration of benzodiazepines in a pharmaceutically acceptable nasal carrier. The carrier may be a saline solution, an alcohol, a glycol, a glycol ether or mixtures thereof.

In PCT WO 91/16929 of Novo Nordisk, glycofurols or ethylene glycols are suggested as carriers for a variety of drugs, including benzodiazepines, which may be used on mucous membranes.

Another solution proposed to this problem, has been the use of micelles or liposomes, but these are frequently difficult to produce on a technical scale.

A further constraint concerning nasal administration is that a small administration volume is required; it is not generally possible to administer more than about 0.1 ml per dose per nostril. Therefore, a great need exists for solvents, in which, on the one hand the solubility of the active drug is high, and which, on the other hand, are non-irritating to the mucosa.

The aim of the present invention is to provide a solution to the above mentioned problems.

Tocopherols and their derivatives such as esters for example, are widely used in vitamin supplementation and as antioxidants in the food industry and in many pharmaceutical compositions. However, although in a few cases, a potential use in formulating pharmaceutical compositions has been reported, tocopherols and derivatives thereof have not generally previously been proposed as drug carriers.

Thus for example, European Patent Application No. 539,215 of Stafford-Miller suggests a possible use of Vitamin E and its derivatives as penetration enhancers in topical compositions.

WO 89/03689 of The Liposome Co., describes a liposome system based on acid derivatives of α-tocopherol in a low pH aqueous medium for delivery of drugs which tolerate, or require, acid conditions.

The present invention is based on the surprising observation that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues.

As will be described in more detail below, it has also been found that certain tocopherol derivatives are efficient, non-irritant emulsifiers for such drugs, when dissolved in a tocopherol-based solvent.

In one aspect, the present invention thus provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions.

A further aspect of the invention provides a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent, comprising said agent dissolved in a tocopherol or a derivative thereof.

Tocopherols are a range of natural and synthetic compounds, also known by the generic term Vitamin E. α-Tocopherol (chemical name: 2,5,7,8-tetramethyl-2-(4',8',12'-trimethyldecyl)-6-chromanole) is the most active and widely distributed in nature, and has been the most widely studied. Other members of the class include beta, gamma, and delta tocopherols but these are not used in pure form in therapeutics, although they are present in foodstuffs. Tocopherols occur in a number of isomeric forms, the D and DL forms being most widely available.

As used herein, the term "tocopherol" includes all such natural and synthetic tocopherol or Vitamin E compounds.

The melting point of natural α-tocopherol is between 2.5 and 3.5° C. α-Tocopherol is a viscous oil at room temperature, is soluble in most organic solvents, but insoluble in water.

Although tocopherols are available naturally in foodstuffs and may be extracted from plants, α-tocopherol is now mainly produced synthetically.

Any of the forms or isomers of tocopherols and their derivatives, eg. esters may be used according to the present invention. Thus for example, α-tocopherol can be used as such or in the form of its esters such as α-tocopherol acetate, linoleate, nicotinate or hemi succinate-ester, many of which are available commercially.

A special article of commerce is called Tenox GT-2 and consists of 70% tocopherol of natural origin, which has been concentrated from vegetable oil. This oil has a mild odour and a gentle taste.

The compositions of the present invention are particularly suited for application to mucous membranes in animals or humans, to deliver systemically substantially insoluble or sparingly soluble biologically active agents in a manner which ensures that a clinical effect is reached at least as rapidly as by conventional oral administration, with for instance tablets.

Thus, the compositions of the invention may be used for controlled release delivery of bioactive agents to achieve a beneficial or therapeutic effect over a prolonged period of time.

The compositions of the invention may also be applied to achieve a local effect, where desired, on the mucous membranes or the underlying tissue.

However, whilst the beneficial effects of the invention are particularly apparent in transmucosal delivery, the utility of the invention is not limited and compositions according to the invention may also be administered topically to all body surfaces, including the skin and all other epithelial or serosal surfaces, as well as parenterally or enterally, eg. as implants or by intravenous, intramuscular or subcutaneous injection, by infusion, or orally.

Transmucosal delivery is preferred however, and compositions according to the invention may be administered to mucosal membranes for example in the nose, vagina, rectum, ears, eyes, oral cavity, lungs, genito-urinary tracts, and gastro-intestinal tract. Nasal, rectal and oral cavity administrations are particularly preferred.

The compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent. However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application.

Viscosity can be reduced by addition of co-solvents such as ethanol, but this is less desired, since solutions of this kind tend to be irritating to certain mucosal tissues.

Alternatively, the tocopherol solutions may be emulsified, to obtain formulations of lower viscosity. This may be achieved in known manner, by mixing the tocopherol-based "oil phase" containing the dissolved bioactive agent with an appropriate aqueous phase, eg. water, saline or buffer solutions.

Methods and appropriate aqueous media for obtaining emulsions are well known in the art and described in the literature. Emulsions according to the invention may be oil-in-water (O/W) or water-in-oil (W/O) emulsions. Generally speaking, O/W emulsions may be achieved when the oil phase contains up to about 70% lipids. W/O emulsions are formed when the oil phase exceeds e.a. 70%.

For nasal administration, due to the small administration volume required, it has generally been found that a high concentration of the oil (or lipid) phase is required. Emulsions with high lipid content are technically difficult to achieve and may be unstable. It may therefore be necessary to employ an emulsifier in order to form a stable emulsion. A wide range of emulsifiers are well known, both in the food and pharmaceutical arts, and are widely described in the literature. However, stability and viscosity may still be a problem, where very high contents of the oil phase are required. Moreover, some of the more widely available commercial emulsifiers, eg. phospholipids, polysorbates or various sorbitan esters of fatty acids may be irritating to the more sensitive mucosal tissues, such as those of the nose.

The inventors have surprisingly found however that tocopherol derivatives, particularly certain esters, may themselves form efficient, non-irritating emulsifiers to enable stable emulsions to be formed, even where high lipid levels are involved eg. about 50–70%. Particular mention may be made in this regard of Vitamin E TPGS which is a water soluble derivative of Vitamin E and consists of α-tocopherol, which is esterified with succinic acid, the other acidic group of the latter being esterified with polyethylene glycol 1000. Vitamin E TPGS is an almost odourless waxy amphiphilic substance with a molecular weight about 1513. The melting point is about 36° C. and its solubility in water is about 20%.

Stable emulsions may readily be achieved according to the invention using a range of tocopherols or derivative compounds as solvents, with Vitamin E TPGS as emulsifier, and any suitable aqueous medium.

A further aspect of the invention thus provides a composition suitable for delivery of substantially insoluble or sparingly soluble biologically active agents, comprising a tocopherol or a derivative thereof, and Vitamin E TPGS as emulsifier.

The tocopherol derivative emulsifier of the invention may be used alone or in conjunction with other known emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers.

It has furthermore surprisingly been shown that various other solvents may be used in the emulsion system described above, without compromising the stability of the emulsion.

When the emulsion according to the present invention is of the oil-in-water type, it is desirable that the droplet size is as small as possible. It has been shown that by using systems according to the invention, for example, α-tocopherol, water, Vitamin E TPGS and bioactive agent, it is possible to form stable emulsions with an initial droplet size in the range 0.01–100 pm, preferably 0.01–50 μm, most preferably 0.1–20 μm.

The compositions which may be prepared according to the present invention, may contain any biologically active agent which is insoluble or sparingly soluble in water, ie.

with a solubility in water (w/v) which is 3% or less. For example such agents may include any bioactive agent which has less than 1% (w/v) solubility in water. Representative active agents from a range of different therapeutic groups are listed below, by way of exemplification.

Hormones and hormone-like substances of the steroid-group:

Corticosteroids such as cortisone, hydrocortisone, prednolone, prednisolone, triamcinolone acetonide, dexamethasone, flunisolide, budesonide, toxicorole pivalate, betametasone, beclomethasone dipropionate, fluticasone etc;

Sex-hormones such as: estradiol, progesterone, testosterone etc;

Antibiotics: Tetracyclines such as tetracycline, doxycycline, oxytetracycline, chloramphenicol etc; Macrolides such as erythromycin and derivatives, etc;

Antivirals: such as acyclovir, idoxuridine, tromantadine etc;

Antimycotics: Miconazole, ketoconazole, fluconazole, itraconazole, econazole, terconazole, griseofulvin, and polyenes such as amphotericin B or nystatine etc;

Anti-amoebics: Metronidazole, metronidazole benzoate and tinidazole etc;

Anti-inflammatory drugs: NSAID's such as indomethacin, ibuprofen, piroxicam, diclofenac etc;

Anti-allergics: Disodium cromoglycate etc;

Immunosuppressive agents: cyclosporins etc;

Coronary drugs: including vasodilators such as nitroglycerin, isosorbide dinitrate, Calcium-antagonists such as verapamile, nifedipine and diltiazem, Cardiac-glycosides such as digoxine.

Analgesics: eg. morphine, buprenorphine, etc;

Local anaesthetics: eg. lidocaine, etc;

Anxiolytics, sedatives & hypnotics: diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lormetazepam, brotizolam, clobazam, clonazepam, lorazepam, oxazepam, buspirone, etc;

Migraine relieving agents: sumatriptan, ergotamines and derivatives etc;

Drugs against motion sickness: eg. cinnarizine, anti-histamines, etc;

Anti-emetics: eg. ondansetron, tropisetron, granisetrone, metoclopramide, etc.

Others: such as disulfiram, vitamin K, etc.

The emulsions according to the present invention are especially suitable for nasal application because of their low index of irritability and are therefore particularly well suited to the delivery of biologically active drugs influencing the central nervous system (CNS).

Other biologically active agents which may be used include peptides, hormones, etc. The active substance may be present in an amount of from about 0.0001% to 50% of the total composition, preferably 0.001% to 40% (w/w).

Generally speaking compositions of the invention may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative solvent. The emulsion used in compositions of the invention may contain 1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w).

As mentioned above, the emulsions of the present invention can be prepared by conventional means, by heating the oil and aqueous phases separately, and then mixing the two phases. The active ingredient can be dissolved in the lipid fraction of the tocopherol solvent and other solvents may be added if desired. The emulsifier, eg. Vitamin E TPGS, and optionally other emulsifiers, can be added to either the oil and/or the water phase. The water phase is then vigorously mixed with the oil phase. Mixing, eg. stirring may be continued as required eg. for up to 2 hours. Depending on the viscosity of the emulsion, a magnetic stirrer, a low shear mixer or the like can be used. If necessary, the emulsion can be processed by a low shear mixer and a high pressure homogenizer to achieve the desired droplet size. The formulations may be inspected microscopically to measure the droplet size and to be sure that no precipitation has taken place. The type of emulsion formed may be determined readily by a colour test using an oil- and/or water-soluble dye. To confirm the result, it may be examined whether the emulsion is easy to wash off with water or not. An O/W emulsion is coloured with the water-soluble dye and is very easy to wash off with water. A W/O emulsion is coloured with the oil-soluble dye and is very difficult to wash off with water.

In a further aspect, the present invention thus provides a method of preparing a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent, said method comprising dissolving said agent in an amount of a tocopherol or a derivative thereof, sufficient to dissolve said agent.

In a preferred aspect, the method of the invention further comprises forming an emulsion of said tocopherol/biologically active agent solution, by mixing with an aqueous phase, optionally in the presence of an emulsifier, preferably vitamin E TPGS.

The compositions of the invention may take any of the conventional pharmaceutical forms known in the art, and may be formulated in conventional manner, optionally with one or more pharmaceutically acceptable carriers or excipients. Thus for example the compositions may take the form of ointments, creams, solutions, salves, emulsions, lotions, liniments, aerosols, sprays, drops, pessaries, suppositories, tablets, capsules or lozenges.

In a still further aspect, the present invention provides the use of a tocopherol or a derivative thereof for the preparation of a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent to a human or non-human animal subject.

Alternatively viewed, the invention can be seen to provide a method of treatment of a human or non-human animal subject by delivery of a substantially insoluble or sparingly soluble biologically active agent, said method comprising administering to said subject a composition of the invention as hereinbefore defined.

The formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired. Thus for example, the following co-solvents may be added:

Vegetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin.

To optimize the stability of the emulsions, it may be appropriate to add surfactants such as Vitamin E TPGS poloxamers (eg. Pluronic®), cetearyl glucoside, polysorbates or sorbitan esters of fatty acids, or any of the other surfactants well known in the art, or other stabilisers such as xanthan gum, or propylene glycol alginate.

It is also possible to enhance the bioadhesive properties of the formulations according to the present invention by addition of bioadhesive polymers such as:

polyacrylic polymers such as carbomer and carbomer derivatives, eg. Polycarbophil or Carbopol etc;

cellulose derivatives such as hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropyl-cellulose or sodium carboxymethylcellulose etc;

natural polymers like gelatin, sodium alginate, pectin etc; more generally, any physiologically acceptable polymer showing bioadhesive characteristics may be used.

To ensure that the formulations have a reasonable shelf-life it may be desirable to include preservatives such as benzalkonium chloride, sodium edetate, sorbic acid, potassium sorbate, phenoxyethanol, phenetanol, parabens or others known in the art. Addition of odour- or taste-masking compounds can also be desirable.

The invention will now be described in more detail in the following non-limiting Examples, with reference to the drawings in which:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing mean serum concentrations (ng/ml) against time (minutes) after intranasal administration of 2.5 mg diazepam (Formulation C) -▲- Desmethyldiazepam -■- Diazepam;

FIG. 2 is a graph showing mean serum concentrations (ng/ml) against time (minutes) after oral administration of 2.0 mg diazepam (Formulation D) -■- Desmethyldiazepam -◆- Diazepam;

EXAMPLES

As already mentioned, administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 μl). The first example has a very high concentration of diazepam, and it is possible to administrate diazepam to the nose and to achieve a rapid clinical effect.

Example 1

A diazepam nosedrop preparation is made as follows: (100 g)

5 g of diazepam is mixed with 44 g of Tenox GT2, and 22 g of triacetin, and 5 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.45 g of Pluronic F-68 (poloxamer 188) and 0.01 g of benzalkonium chloride are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed into the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion was a pale yellow o/w emulsion, where the mean droplet size was about 1–2 μm.

This formulation (1) was tested in 8 rabbits in a randomized cross-over study compared with a commercially available diazepam formulation, Stesolido 5mg/ml for injection, (2).

Formulation 1 was given intranasally (i.n.) with a Eppendorf Multipette® 4780. Each rabbit was held in a supine position during and one minute after i.n. dosing in one nostril. The rabbits receive a volume that equals 2 mg diazepam, 40% of formulation 1. After each administration the actual dose received is estimated by visual inspection of the pipette tip and the rabbit nostrils. Only applications volumes estimated to 80% are accepted.

Formulation 2 was given as an ear-vein infusion during M minute. The rabbits received 0.4 ml Stesolid® 5 mg/ml (equals 2 mg diazepam). The rabbits were placed in a supine position for half a minute to attain the same experimental conditions as for i.n. dosing.

The rabbits were then tested with respect to pharmacodynamic response in the following way:

Hind legs to one side and the rabbit must stay in this position even after a firm tip with a finger on the hip. The test is immediately repeated with both legs placed on the other side.

The rabbits were tested approximately once per minute until positive pharmacodynamic response, and thereafter tested every 2 minutes. Total test period is 20 minutes. The same person has dosed and tested all the rabbits in the present study.

The time to pharmacodynamic response is 4.4 minutes (mean, n=8) using formulation 1 and 1.6 minutes (mean, n=8) using formulation 2.

Example 2

A diazepam nosedrop preparation is made as follows: (100 g)

5 g of diazepam is mixed with 45.4 g of Tenox GT2, and 22.7 g of triacetin, and 15 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.45 g of Pluronic F-68 (poloxamer 188) and 0.01 g of benzalkonium chloride are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a clear orange w/o emulsion.

A less concentrated formulation of diazepam is required for the rectal administration, but still it can be very difficult to find an acceptable vehicle with low irritation.

Example 3

A diazepam enema preparation is made as follows: (100 g)

1 g of diazepam is mixed with 40 g of (-tocopherol, and 15 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. 5 g of ethanol is added to the oil phase immediately before mixing with the water phase. To the water phase, 2.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a white o/w emulsion.

Cinnarizine is used for motion sickness. Like diazepam, the drug has a very low water solubility. It will be a great advantage if the patient can administer the drug easily and have a rapid effect.

Example 4

A cinnarizine nosedrop formulation is made as follows: (100 g)

5 g of cinnarizine is mixed with 64 g of α-tocopherol, and 8 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a white o/w emulsion.

Miconazole is used for the local treatment of infections caused by fungi. The next two formulations show formulations for use in the oral cavity and the vagina.

Example 5

A miconazole preparation for the oral cavity is made as follows: (100 g)

20 g of miconazole is mixed with 58.8 g of α-tocopherol, and 13 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. 5 g of ethanol is added to the oil phase immediately before mixing with the water phase. To the water phase, 1.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is added very slowly to the oil phase under vigorously mixing by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a yellow to brown w/o emulsion.

Example 6

A miconazole vaginal cream is made as follows: (100 g)

5 g of miconazole is mixed with 38 g of α-tocopherol, and 38 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 2.5 g of Pluronic F-681 (poloxamer 188) and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a low shear mixer. Thereafter, the emulsion is cooled to room temperature still mixed by the low shear mixer. The emulsion is a glossy, beige w/o emulsion. The emulsion has a consistency as an ointment and is very sticky.

The following Examples are divided into three subsections covering 1) Solubility; 2) Compositions and 3) Pharmacology/toxicology.

Example 7

Solubility

For the following, non-limiting, sparingly soluble drugs in water, the solubility in α-tocopherol and sesame oil are listed in Table 1:

Sesame oil was chosen as the reference, because it is a very commonly used and well tolerated vegetable oil. The solubilities in sesame oil and α-tocopherol were investigated by visual inspection of the saturation point.

TABLE 1

Active agent	g drug in 100 g of α-tocopherol	g drug in 100 g of sesame oil
Diazepam	12	2
Alprazolam	4 <x< 6	<0.2
Midazolam	>13	1 <x< 2
Cinnarizine	11 <x< 18	2 <x< 4
Metoclopramide	2 <x< 4	<2
Budesonide	1 <x< 2	<0.1
Miconazole	60	5 <x< 10
Metronidazole benzoate	12 <x< 14	<2
Lidocaine	>45	>18
Disulfiram	5	3 <x< 4
Progesterone	>30	2 <x< 4
Testosterone	16 <x< 18	0.6 <x< 1

All the investigated biologically active agents show a surprisingly high solubility in α-tocopherol.

Compositions

In the following, non-limiting Examples, several drugs are shown in a number of different types of administration forms.

The emulsions were prepared as follows:

The oil and the water phase were heated slowly until homogeneous phases were achieved.

The warm water phase was vigorously mixed into the oil phase. Then, the emulsion was slowly cooled to room temperature while stirring. The emulsion may be homogenized.

The preparation of the solutions was made as simple solution, in which the preparations were stirred until the drug was completely dissolved.

As already mentioned, administration of drugs with low water solubility to the nose is very difficult, because of the limited acceptable volume for the nose (about 100 μl). The following examples have very high concentration of diazepam, so it was possible to administer diazepam to the nose and to get a fast clinical effect.

Example 8

An O/W emulsion of diazepam as a nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α-Tocopherol	59.000 g
	Vitamin E TPGS.	5.000 g
Water phase:	Disodium edetate	0.050 g
	Potassium sorbate	0.200 g
	Xanthan gum	0.025 g
	purified water to	100.000 g

The water phase was adjusted to pH 4.7 by 1N HCl.

Example 9

An O/W emulsion of diazepam as nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α-Tocopherol	58.000 g
	Sorbitan trioleate	0.500 g
	Fractionated coconut oil	5.000 g
Water phase:	Potassium sorbate	0.200 g
	Poloxamer 188	1.000 g
	Xanthan gum	0.030 g
	Polysorbate 80	0.500 g
	Purified water to	100.000 g.

The water phase was adjusted to pH 4.5 by 2N HCl.

Example 10

An O/W emulsion of diazepam as nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α-Tocopherol	50.000 g
	Triacetin	10.000 g
	Cetearyl glucoside	2.000 g
	Methylparahydroxybenzoate (MPHB)	0.080 g
	Propylparahydroxybenzoate (MPHB)	0.040 g
Water phase:	Poloxamer 188	3.000 g
	Xanthan gum	0.030 g
	Purified water to	100.000 g.

Example 11

A solution of diazepam, eg. as nosedrop, (25 g):

Diazepam	1.250 g
α-Tocopherol	10.000 g
Triacetin	13.750 g

A less concentrated formulation of diazepam is needed for the rectal administration, but still it can be very difficult to find an acceptable vehicle with low irritation.

Example 12

A solution of cinnarizine, eg. as drops for administration to the oral cavity (25 g):

Cinnarizine	1.250 g
α-tocopherol	17.500 g
ethanol	1.250 g
fractionated coconut oil	5.00 g

A study has shown, that cinnarizine has a higher oral bioavailability, if it is dissolved in a vehicle before administration, [J. Pharm. Sci., vol 76, no. 4, p. 286–288, 1987], an example of such a vehicle could be α-tocopherol.

Example 13

A solution of cinnarizine, eg. for oral administration in capsules, (25 g):

Cinnarizine	0.750 g
α-Tocopherol	24.250 g

Miconazole is used locally for treatment of infections caused by fungi. The following examples show formulations for the oral cavity and the vagina.

Example 14

A solution of miconazole e. g. as drops for administration to the oral cavity (25 g).

Miconazole	6.250 g
α-Tocopherol	16.875 g
Ethanol	1.875 g

Budesonide is a very potential drug, and is used as a local corticoid, e. g. for rhinitis.

Example 15

An O/W emulsion of budesonide as nosedrop or nasal spray (50 g).

Oily phase:	Budesonide	0.025 g
	α-tocopherol	12.500 g
	Vitamin E TPGS	5.000 g
Water phase:	Potassium sorbate	0.100 g

-continued

	Xanthan gum	0.020 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Example 16

A solution of budesonide as nosedrop (25 g).

Budesonide	0.025 g
α-tocopherol	10.000 g
Sesame oil	14.975 g

Alprazolam is a benzodiazepine which is used for the treatment of e. g. anxiety, therefore a rapid effect is desired in a easy way.

Example 17

An o/w emulsion of alprazolam as nosedrop or nasal spray (100 g).

Oily phase:	Alprazolam	0.500 g
	α-tocopherol	20.000 g
	Vitamin E TPGS	10.00 g
Water phase:	Potassium sorbate	0.200 g
	Xanthan gum	0.050 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Example 18

A solution of alprazolam, e.g. as drops for administration in the oral cavity (25 g).

alprazolam	0.125 g
α-tocopherol	13.750 g
sesame oil	11.125 g

Midazolam is a benzodiazepine tranquiliser with a sedative effect e.g., and is used for the treatment of anxiety and tension states, and as a sedative and for premedication. Midazolam has a very high first-pass effect after oral administration.

Example 19

An O/W emulsion of midazolam as nosedrop (50 g).

Oily phase:	Midazolam	1.250 g
	α-Todopherol	29.500 g
	Vitamin E TPGS	2.500 g
Water phase:	Potassium sorbate	0.100 g
	Xanthan gum	0.013 g
	Poloxamer 188	0.750 g
	Disodium edetate	0.025 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Disulfiram is used in the treatment of chronic alcoholism.

Example 20

A solution of disulfiram, e. g. as an oral solution or for oral administration by capsules (25 g).

Disulfiram	1.125 g
α-Tocopherol	23.875 g

Example 21

An O/W emulsion of lidocaine for treatment of e.g. insect bites (100 g).

Oily phase:	Lidocaine	5.000 g
	α-Tocopherol	40.000 g
	Cetearyl glucoside	4.000 g
	MPHB	0.080 g
	PPHB	0.040 g
Water phase:	Poloxamer 188	3.000 g
	Xanthan gum	0.030 g
	Purified water to	100.000 g

Example 22

Pharmacology

Studies on Rabbits

Preparations containing CNS active and muscle relaxing drugs such as diazepam and midazolam were tested in a pharmacodynamic model in rabbits.

The model consists of the following tests:

Test 1:

Hind legs to one side and the rabbit must stay in this position even after a firm tip with a finger on the hip. The test is immediately repeated with both legs placed on the other side.

Test 2:

Hind legs stretched out backwards and the rabbit must stay in this position even after a firm tip with a finger on the hip.

Test 3:

The rabbit must stay in a supine position, when placed in such a position.

After administration of the formulations (i.n., oral or i.v.) the rabbits were exposed to the three tests approximately once per minute until positive pharmacodynamic response, and thereafter every 2 minutes. The total test period was 20 minutes after i.n. and i.v. administration and 30 minutes after peroral administration.

The time elapsed from administration until the first positive response in test 1 was used to compare the onset of action of the different formulations.

Study 1

This pharmacodynamic study compared the nasal formulation of Example 8 (C) containing 5% of diazepam to a commercially available diazepam formulation, Stesolido 2mg tablet, Dumex (D). The study was run in 8 rabbits in a randomized cross-over study. The rabbits were tested for pharmacodynamic response as described previously, but the test period was 30 minutes after peroral administration to be sure to obtain a pharmacodynamic effect.

Formulation C was given intranasally (i.n.) with a laboratory pipette. Each rabbit was held in a supine position during and one minute after i.n. dosing in one nostril. The rabbits received a volume equivalent to 2.5 mg diazepam. After each administration the actual dose received is calculated by subtraction of the weight of the pipette before and after administration. Only applications determined to 80% (2 mg diazepam) were accepted.

Formulation D was given as an oral administration using a stomach pump. The tablet was dissolved in 5 ml water immediately before administration. The tube was rinsed with 10 ml water.

The time to onset of pharmacodynamic response in test 1 is 4.5 minutes (median, n=7) using formulation C and 19.4 minutes (median, n=8) using formulation D.

Study 2

This pharmacokinetic study compared the nasal formulation of Example 8 (C) containing 5% of diazepam to a commercially available diazepam formulation, Stesolido 2mg tablet, Dumex (D). The study was run in 8 rabbits in a randomized cross-over study.

Formulation C was given intranasally (i.n.) as described in study 1.

Formulation D was given by oral administration as described in study 1 using a stomach pump.

Blood samples from the ear-vein were taken before administration (time=0) and at 2, 5, 10, 15, 30, 45, 60, 75, 90, 120, 180 and 240 minutes.

Serum was analyzed for diazepam and the metabolite, desmethyldiazepam using Gas Chromatografy (GC). The limit of detection was 5ng/ml for both substances.

The pharmacokinetic parameters found for diazepam were t_{max}=23 minutes (median, n=6), C_{max}=68.2 ng/ml (median, n=6) after administration of formulation C and t_{max}=45 minutes (median, n=6), C_{max}=9.7 ng/ml (median, n=6) after administration of formulation D.

FIGS. 1 and 2 illustrate the mean serum concentrations of diazepam and desmethyldiazepam after administration of formulations C and D.

Study 3

This pharmacodynamic study compared Example 8(C) containing 5% of diazepam with Example 19 (E) containing 2.5% of midazolam. The study was using 6 rabbits.

Formulations C and E were given intranasally (i.n.) with a laboratory pipette. Each rabbit was held in a supine position during and one minute after i.n. dosing in one nostril. The rabbits received a volume equivalent to 2.5 mg diazepam or 1.25 mg midazolam, respectively.

After each administration the actual dose received was calculated by subtraction of the weight of the pipette before and after administration. Only doses equivalent to 80% were accepted.

The time to onset of pharmacodynamic response in test 1 was 3.1 minutes (median, n=6) using formulation C containing diazepam and 2.5 minutes (median, n=6) using formulation E containing midazolam.

Example 23

Toxicology

Local Irritancy in Humans:

The investigation was carried out in order to estimate irritation after nasal application of 10 mg of diazepam; 100 mg of the preparation from Example 8 in each nostril.

6 volunteers, 3 male and 3 female participated in the trial.

The investigator inspected both nostrils macroscopically for local irritation at the following times: Immediately after medication, at 30 minutes, and 1, 2, 4, and 6 hours.

In one volunteer the macroscopic inspection showed light blush of both nostrils immediately after medication. None of the six volunteers had local irritation of the nostrils 30 minutes after application, see table 2.

Conclusion

The total results of the trial have shown that preparation of Example 8 does not cause unacceptable irritation of the nostrils.

TABLE 2

Individual local irritation of the nostrils after intranasal administration of 10 mg diazepam, (Example 8)

	Local irritation											
	Immediately after medication		30 min		1 h		2 h		4 h		6 h	
Volunteer no	R	L	R	L	R	L	R	L	R	L	R	L
1	—	—	—	—	—	—	—	—	—	—	—	—
2	—	—	—	—	—	—	—	—	—	—	—	—
3	—	—	—	—	—	—	—	—	—	—	—	—
4	Light blush	Light blush	—	—	—	—	—	—	—	—	—	—
5	—	—	—	—	—	—	—	—	—	—	—	—
6	—	—	—	—	—	—	—	—	—	—	—	—

R: right nostril
L: left nostril

What is claimed is:

1. A composition for the non-topical delivery of an active agent in the form of a non-liposomal emulsion comprising two phases:

a) a first tocopherol-based phase comprising an active agent which is no more than sparingly soluble in water and which is not a tocopherol; and

an amount of 20% to 95% w/w based on the total weight of the composition of at least one tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof sufficient to dissolve the active agent in the tocopherol-based phase;

b) a second phase comprising an emulsifying agent wherein the emulsifying agent is vitamin E TPGS; wherein said active agent is selected from the group consisting of antibiotics; antivirals; antimycotics; anti-amoebics; non-steroidal anti-inflammatory drugs; anti-allergics; immunosurpressive agents; coronary drugs; analgesics, local anaesthetics; anxiolytics, sedatives and hypnotics; migraine relieving agents; drugs against motion sickness; anti-emetics; disulfiram and vitamin K.

2. A composition as claimed in claim 1 wherein the tocopherol is α-tocopherol or an acetate, linoleate, nicotinate or hemi-succinate derivative thereof.

3. A composition as claimed in claim 1 in a form suitable for transmucosal, peroral, enteral or parenteral application.

4. A composition as claimed in claim 1, in a form of suitable for intranasal, buccal, vaginal or rectal application or for administration via the oral cavity.

5. A composition as claimed in claim 1 wherein the active agent is selected from the group consisting of tetracycline, doxycycline, oxytetracylcline, chloramphenicol, erythromycin, acyclovir, idoxuridine, tromantadine, miconazolc, ketoconazole, fluconazole, itraconazole, econazole, griseofulvin, amphotericin B, nystatine, metronidazole, metronidazole benzoate, tinidazole, indomethacin, ibuprofen, piroxicam, diclofenac, disodium cromoglycate, nitroglycerin, isosorbide dinitrate, verapamile, nifedipine, diltiazem, digoxine, morphine, cyclosporins, buprenorphine, lidocaine, diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam lormetazepam, brotizolam, clobazam, clonazepam, lorazepam, oxazepam, busiprone, sumatriptan, ergotamine derivatives, cinnarizine, anti-histamines, ondansetron, tropisetron, granisetrone, metoclopramide, disulfiram, and vitamin K.

6. A composition as claimed in claim 1, wherein the active agent is a coronary drug selected from the group consisting of vasodilators; calcium-antagonists and cardiac-glycosides.

7. A composition as claimed in claim 1, wherein the active agent is a benzodiazepine or an antimycotic.

8. A composition as claimed in claim 1, wherein the active agent is selected from the group consisting of diazepam, midazolam and miconazole.

9. A composition as claimed in claim 1, wherein the amount of the tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof is from 35 to 80% (w/w).

10. A composition as claimed in claim 1, further comprising at least one additional component selected from the group consisting of solvents, surfactants, stabilizers, bioadhesive polymers, preservatives, odor-masking agents and taste-masking agents.

11. A composition for the non-topical delivery of an active agent in the form of a non-liposomal emulsion comprising two phases:

a) a first tocopherol-based phase comprising an active agent which is no more than sparingly soluble in water and which is not a tocopherol; and

an amount of 20% to 95% w/w based on the total weight of the composition of at least one tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof sufficient to dissolve the active agent in the said tocopherol-based phase;

b) a second phase comprising an emulsifying agent wherein the emulsifying agent is vitamin E TPGS.

12. A composition as claimed in claim 11 wherein the active agent is selected from the group consisting of antibiotics; antivirals; antimycotics; anti-amoebics; non-steroidal anti-inflammatory drugs; anti-allergics; immunosuppressive agents; coronary drugs; analgesics; local anaesthetics; anxiolytics, sedatives and hypnotics; migraine relieving agents; drugs against motion sickness; anti-emetics; disulfiram and vitamin K.

13. A composition as claimed in claim 12 wherein the active agent is selected from the group consisting of tetracycline, doxycycline, oxytetracycline, chloramphenicol, erythromycin, acyclovir, idoxuridine, tromantadine, miconazole, ketoconazole, fluconazole, itraconazole, econazole, griseofulvin, amphotericin B, nystatine, metronidazole, metronidazole benzoate, tinidazole, indomethacin, ibuprofen, piroxicam, diclofenac, Disodium cromoglycate, nitroglycerin, isosorbide dinitrate, verapamile, nifedipine, diltiazem, digoxine, morphine, cyclosporins, buprenorphine, lidocaine, diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lormetazepam, brotizolam, clobazam, clonazcpam, lorazepam, oxazepam, busiprone, sumatriptan, ergotamine

derivatives, cinnarizine, anti-histamines, ondansetron, tropisetron, granisetrone, metoclopramide, disulfiram, and vitamin K.

14. A composition as claimed in claim **11** wherein the tocopherol is α-tocopherol or an acetate, linoleate, nicotinate or hemi-succinate derivative thereof.

15. A composition as claimed in claim **11** in a form suitable for transmucosal, peroral, enteral or parenteral application.

16. A composition as claimed in claim **11**, in a form suitable for intranasal, buccal, vaginal or rectal application or for administration via the oral cavity.

17. A composition as claimed in claim **11**, wherein the active agent is a coronary drug selected from the group consisting of vasodilators; calcium-antagonists and cardiac-glycosides.

18. A composition as claimed in claim **11**, wherein the active agent is a benzodiazepine or an antimycotic.

19. A composition as claimed in claim **11**, wherein the active agent is selected from the group consisting of diazepam, midazolam and miconazole.

20. A composition as claimed in claim **11**, wherein the amount of the tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof is from 35 to 80% (w/w).

21. A composition as claimed in claim **11**, further comprising at least one additional component selected from the group consisting of solvents, surfactants, stabilizers, bioadhesive polymers, preservatives, odor-masking agents and taste-masking agents.

22. A composition for the parenteral delivery of an active agent in the form of a non-liposomal emulsion comprising two phases:

a) a first tocopherol-based phase comprising an active agent which is no more than sparingly soluble in water and which is not a tocopherol; and

an amount of 20% to 95% w/w based on the total weight of the composition of at least one tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof sufficient to dissolve the active agent in the tocopherol-based phase;

b) a second phase comprising an emulsifying agent wherein the emulsifying agent is vitamin E TPGS.

23. A composition as claimed in claim **22** wherein the active agent is selected from the group consisting of antibiotics; antivirals; antimycotics, anti-amoebics; non-steroidal anti-inflammatory drugs; anti-allergics; immunosuppressive agents; coronary drugs; analgesics, local anaesthetics; anxiolytics, sedative and hypnotics; migraine relieving agents; drugs against motion sickness; anti-emetics; disulfiram and vitamin K.

24. A composition as claimed in claim **23** wherein the active agent is selected from the group consisting of tetracycline, doxycycline, oxytetracycline, chloramphenicol, erythromycin, acyclovir, idoxuridine, tromantadine, miconazole, ketoconazole, fluconazole, itraconazole, econazole, griseofulvin, amphotericin B, nystatine, metronidazole, metronidazole benzoate, tinidazole, indomethacin, ibuprofen, piroxicam, diclofenac, Disodium cromoglycate, nitroglycerin, isosorbide dinitrate, verapamile, nifedipine, diltiazem, digoxine, morphine, cyclosporins, buprenorphine, lidocaine, diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lormetazepam, brotizolam, clobazam, clonazepam, lorazepam, oxazepam, busiprone, sumatriptan, ergotamine derivatives, cinnarizine, anti-histamines, ondansetron, tropisetron, granisetrone, metoclopramide, disulfiram, and vitamin K.

25. A composition as claimed in claim **22** wherein the tocopherol is α-tocopherol or an acetate, linoleate, nicotinate or hemi-succinate derivative thereof.

26. A composition as claimed in claim **22**, wherein the active agent is a coronary drug selected from the group consisting of vasodilators; calcium-antagonists and cardiac-glycosides.

27. A composition as claimed in claim **22**, wherein the active agent is a benzodiazepine or an antimycotic.

28. A composition as claimed in claim **22**, wherein the active agent is selected from the group consisting of diazepam, midazolam and miconazole.

29. A composition as claimed in claim **22**, wherein the amount of tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof is from 35 to 80% (w/w).

30. A composition as claimed in claim **22**, further comprising at least one additional component selected from the group consisting of solvents, surfactants, stabilizers, bioadhesive polymers, preservatives, odor-masking agents and taste-masking agents.

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Exhibit H

US006241969B1

(12) **United States Patent**
Saidi et al.

(10) **Patent No.: US 6,241,969 B1**
(45) **Date of Patent: Jun. 5, 2001**

(54) **AQUEOUS COMPOSITIONS CONTAINING CORTICOSTEROIDS FOR NASAL AND PULMONARY DELIVERY**

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(58) **Field of Search** 424/450, 45, 198.1; 514/179, 180

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(57) **ABSTRACT**

The present invention provides compositions containing corticosteroid compounds as active agents for the treatment of ailments and diseases of the respiratory tract, particularly the lungs, by way of nasal and pulmonary administration. The corticosteroid compounds are present in a dissolved state in the compositions. The compositions can be formulated in a concentrated, essentially non-aqueous form for storage or in a diluted, aqueous-based form for ready delivery. In a preferred embodiment, the corticosteroid composition contains an ethoxylated derivative of vitamin E and/or a polyethylene glycol fatty acid ester as the high-HLB surfactant present in the formulation. The compositions are ideally suited for inhaled delivery with a nebulizer or for nasal delivery.

29 Claims, No Drawings

AQUEOUS COMPOSITIONS CONTAINING CORTICOSTEROIDS FOR NASAL AND PULMONARY DELIVERY

FIELD OF THE INVENTION

The present invention relates to pulmonary drug delivery compositions useful for the inhaled administration of corticosteroid compounds and the method of their administration. The delivery compositions are useful for the treatment of ailments and diseases of the lungs. Similar corticosteroid compositions may be used for nasal delivery.

BACKGROUND OF THE INVENTION

Delivery of therapeutic compounds directly to affected lung tissues has several advantages. The drug reaches the target tissue without first entering the systemic circulation and being subjected to dilution by the blood, binding to blood components, or metabolism by the liver and excretion by the kidneys. A high local concentration of drug can be achieved in the lungs while the systemic concentration is kept below that likely to cause adverse side effects. In addition, the apical side of the lung tissue—the side exposed directly to inspired air—can be treated with compounds that might not readily cross the endothelium or epithelium, which form barriers between the apical surface and the blood plasma. Similar considerations apply to the tissues lining the nasal passages and sinus cavities.

Several means have been developed to deliver compounds directly to the passages of the lung or nose. The most common form, especially for water-insoluble drugs, is a powder suspension that is propelled into the mouth while the patient inhales.

Propulsion is accomplished by use of pressurized gas or by any of a variety of mechanical means of entraining a fine powder into a gas or air stream. Common devices for this purpose include metered dose inhalers (MDIs), turbo inhalers, and dry powder inhalers. Each of these uses a different means of propulsion; however, a common characteristic is that once the therapeutic drug leaves the device it is, or becomes, a fine powder. In an MDI, the drug may be suspended or solubilized in a non-aqueous propellant, which is typically a chlorofluorocarbon or fluorinated hydrocarbon that is a liquid under pressure at room temperature. In turbo inhalers and dry powder inhalers, the drug is present in the form of a micronized powder.

The particle size distribution of the aerosolized drug compositions is very important to the therapeutic efficacy of the drug when delivered by inhalation. Studies of inhaled aerosols indicate that particles or droplets of greater than about 5 micrometers in mean acrodynamic diameter are effectively excluded from entry into the lungs and are captured in the nasal passages or throat and swallowed instead. Thus, the drug compounds delivered by these devices must be formulated in such a way that the mass median aerodynamic diameter (MMAD) is below 5 micrometers. In addition, even smaller particle sizes, on the order of 0.5 to 2.5 micrometers, are needed if the drug is to reach the alveolar sacs deep in the lungs. However, particles with aerodynamic diameter less than about 0.5 micrometers are likely to be exhaled before the drug is totally deposited on the lung surface.

Additional considerations for the use of powder-type drug delivery devices for inhalation include the limited amount of drug that can be contained in one or two puffs from the device and the need for the user to skillfully coordinate hand activation of the device with inhalation. This latter limitation

is particularly important for those patients who are disabled, children, or elderly.

Nebulizers offer an alternative method of administering therapeutic agents to the lungs. These devices work by means of an air jet or an ultrasonic pulse that is applied to a solution producing a fine mist. Therapeutic agents dissolved or suspended in the solution can be incorporated into the mist. The patient then breathes the mist in and out over the course of several minutes of treatment, during which 1 to 3 mL of the drug formulation is typically nebulized. Considerations of particle size mentioned above also apply to the droplet size of the mists. However, it is possible to rebreathe a portion of the mist during several minutes of treatment and increase the capture of the fine droplet fraction that can penetrate the lung most deeply. In addition, there is no need for coordination between hand action and breathing, making the nebulizer easier to use for patients. It may be possible, in some cases, to administer drugs not soluble in aqueous solution by nebulizing them in suspension. However, the droplet size of nebulized drug-containing suspensions cannot be smaller than that of the suspended particles. Therefore, the finer droplets produced from these systems would not contain any drug.

Thus, one limitation of nebulized formulations is that they are most suitable for those drug compounds that are sufficiently water soluble such that a therapeutic dose of the drug can be dissolved in from 1 to about 3 mL of aqueous solution. One way around this limitation is to formulate with polar organic solvents or aqueous solutions thereof. However, few organic solvents can be safely inhaled for prolonged periods. Most organic solvents that are currently approved for use in inhalation devices are propellants, such as chlorofluorocarbons (CFCs), which will soon be eliminated from manufacturing for environmental reasons, or the newer hydrofluorocarbons and low boiling hydrocarbons, all of which are expected to evaporate prior to penetrating the lungs. Such solvents can evaporate rapidly during nebulization and leave the drug behind in the device or in large particles that would be likely to be deposited in the mouth or throat rather than be carried to the lungs. Indeed, MDIs were developed to circumvent such problems.

Another way to overcome the solubility problem of the drug is to blend cosolvents such as ethanol, propylene glycol, or polyethylene glycol with water. However, there are limits to acceptable levels of these cosolvents in inhaled products. Typically, the cosolvents make up less than about 35% by weight of the nebulized composition, although it is the total dose of cosolvent as well as its concentration that determines these limits. The limits are set by the propensity of these solvents either to cause local irritation of lung tissue, to form hyperosmotic solutions which would draw fluid into the lungs, and/or to intoxicate the patient. In addition, most potential hydrophobic therapeutic agents are not sufficiently soluble in these cosolvent mixtures.

Thus, there is a need to develop improved systems that can solubilize water-insoluble drugs for nebulization, and to minimize the levels of cosolvent necessary to accomplish this. The ideal system would have a cosolvent concentration below about 15% and in certain cases below about 5%. It would consist of non-toxic ingredients and be stable for long periods of storage at room temperature. When nebulized, it would produce droplets having an MMAD less than about 5 micrometers.

Droplet size considerations are not as critical for sinus or nasal administration, but it is still important to use safe, non-irritating ingredients. An additional consideration for

both nasal and inhaled delivery is that some of the formulation will inevitably be tasted and swallowed. Therefore, acceptable taste and odor must be considered important parameters, especially for nebulized formulations where exposure is prolonged and where pediatric subjects form an important fraction of the probable patient population.

Anti-inflammatory corticosteroids, which are essentially water-insoluble drugs that act on inflammatory cells in the respiratory mucosa, are a type of therapeutic compounds in need of improved inhaled delivery. These steroids are useful in treating a variety of inflammatory diseases including asthma.

Asthma is a chronic obstructive disease of the lower airways. The major clinical and pathological features of asthma are (partially) reversible airflow limitations due to bronchial constriction, bronchial hyperreactivity to noxious stimuli such as allergens or cold air, and inflammation of the airways. Anti-inflammatory corticosteroids are useful in treating this last condition. They are the most effective group of therapeutic agents currently available for treating allergic asthma. The steroids suppress many inflammatory processes including inhibition of eosinophilia, epithelial shedding, and edema. The cellular basis of these actions is under active investigation.

Like other steroid hormone analogs, corticosteroids bind with high affinity to cytoplasmic receptor proteins in target cells. The receptor-steroid complexes migrate to the cell nucleus, where they interact with nuclear chromatin to control gene expression. The receptor binding is saturable and very small amounts of steroid suffice to elicit maximum cellular responses, including suppression of inflammation.

Anti-inflammatory steroids can act systemically as well as locally. Therefore, while systemic administration of anti-inflammatory steroids will diminish airway inflammation in asthmatics, it can also cause such adverse effects as general immunosuppression and imbalances in mineral metabolism. The corticosteroids commonly used in asthma treatment have a high ratio of topical to systemic potency. That is, these corticosteroids are highly active when delivered directly to the site of inflammation but relatively inactive when passed through the systemic circulation. The portion of an inhaled dose which is swallowed and absorbed through the intestine or absorbed through the lung tissue into the circulation is subjected to metabolism by the liver and converted to less active compounds with short half-lives. These metabolites are quickly eliminated from the blood, reducing the incidence of systemic side effects.

Among the most commonly used steroids are aldosterone, beclomethasone, betamethasone, budesonide, cloprednol, cortisone, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluorometholone, flurandrenolone, fluticasone, halcinonide, hydrocortisone, icomethasone, meprednisone, methylprednisolone, mometasone, parametbasone, prednisolone, prednisone, tixocortol, triamcinolone, and others, and their respective pharmaceutically acceptable derivatives, such as beclomethasone diproprionate, dexamethasone 21-isonicotinate, fluticasone propionate, icomethasone enbutate, tixocortol 21-pivalate, triamcinolone acetonide, and others. Fortunately, some of these synthetic steroids have low potentials for systemic absorption because of their unique structures and metabolism.

Corticosteroids have usually been formulated as suspensions of micronized drug powder in chlorofluorocarbon vehicles or with chlorofluorocarbon-free propellants and delivered by metered dose inhaler. The choice of this type of carrier and apparatus was dictated by the fact that corticosteroids are very difficult to stabilize in aqueous media and frequently produce systems that exhibit crystal growth, precipitation, and/or aggregation of suspended or solubilized drug.

Corticosteroids have been formulated in different drug delivery systems for administration to the respiratory tract. U.S. Pat. No. 5,292,499 relates to reverse micelle colloidal dispersions of hydrophilic pharmaceutically active compounds prepared with acrosol CFC propellant formulations useful for topical, endopulmonary, nasal, or inhalation administration.

U.S. Pat. No. 5,208,226 describes the concept of using a novel combination therapy, which has greater efficacy and duration of bronchodilator action than previously known combinations and that permits the establishment of a twice daily dosing regimen. The effective treatment consists of administration of a stimulant bronchodilator, salmeterol, and/or a physiologically acceptable salt thereof, combined with beclomethasone dipropionate in a form suitable for inhalation such as a metered dose inhaler with dry powder or chlorofluorocarbon-containing formulations.

U.S. Pat. No. 5,474,759 discloses aerosol formulations that are substantially free of chlorofluorocarbons, and having particular utility in medicinal applications. The formulations contain a propellant (such as 1,1,1,2,3,3,3-heptafluoropropane), a medium-chain fatty acid propylene glycol diester, a medium-chain triglyceride, optionally a surfactant, and optionally auxiliary agents such as antioxidants, preservatives, buffers, sweeteners and taste masking agents. These formulations are used as carriers for the delivery of inhaled drugs such as albuterol, momestrasone, isoprenaline, disodium cromoglycate, pentamidine, ipratropium bromide, and salts and clathrates thereof.

Recently, several corticosteroid liposomal formulations have been under development. U.S. Pat. No. 5,192,528 discloses the delivery of corticosteroids by inhalation for treating a variety of lung diseases. The carrier consists of an aqueous suspension of sized liposomes containing the drug. This liposome-entrapped drug form is then aerosolized, using a pneumatic nebulizer, to deliver the drug to the lung. Cholesterol and/or cholesterol sulfate can be incorporated into the system to delay the release of corticosteroid from the liposomes in the lung environment. These formulations have many advantages over microcrystalline formulations, including utilization of otherwise water-insoluble materials, sustained pulmonary release, and facilitated intracellular delivery. However, some general problems pertaining to liposomes regarding manufacturing processes, the use of synthetic phopsholipids (such as dilauroylphosphatidylcholine), and the distribution patterns of aerosolized liposomes in the lung may cause difficulties in the wide application of this type of aerosolized formulation.

There are as yet no marketed, commercial liposomal, micellar, or microemulsion formulations available for pulmonary delivery of corticosteroids.

SUMMARY OF THE INVENTION

The present invention provides compositions suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract and methods for the administration of said compositions.

In one embodiment, the corticosteroid composition contains from about 0.1 to about 20 percent by weight of a high-HLB surfactant component (HLB greater than about 10), for example, ethoxylated derivatives of Vitamin E such as tocopheryl polyethylene glycol 1000 succinate ("TPGS"). The HLB, or hydrophilic-lipophilic balance, is a measure on an arbitrary scale of the polarity of a surfactant or mixture of surfactants. For example, TPGS has an HLB between about 15 and 19. Generally, the corticosteroid composition contains the corticosteroid in an amount from about 5 μg/ml to about 1 mg/ml. The composition is aqueous-based, containing. at least about 70 weight percent of an aqueous phase that can include buffering, tonicity, taste-masking, and preservation additives.

The corticosteroid composition can also contain one or more pharmaceutically acceptable cosolvents to aid in the processing of the composition and to increase the solubility of the corticosteroid. Such cosolvents include mono- and polyvalent alcohols, such as propylene glycol, ethanol, and polyethylene glycol. Optionally, the corticosteroid compositions also can contain such components as low-HLB surfactants (HLB below about 8) and/or oils. Low-HLB surfactants include phospholipids, medium-chain mono- and diglycerides, and mixtures thereof. Useful pharmaceutically acceptable oils include triglycerides and propylene glycol diesters of medium-chain fatty acids.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions containing corticosteroid compounds as active agents for the treatment of ailments and diseases of the respiratory tract, particularly the lungs, by way of nasal and pulmonary administration. The compositions can be formulated such that they contain the corticosteroid active agent(s) in a dissolved state. The formulations can be stored either in a concentrated form to be diluted at the time of use or a ready-for-use, diluted state. The present invention also sets forth methods for using the compositions for nasal or inhaled delivery.

The corticosteroid compositions of the present invention are preferably formulated with ethoxylated derivatives of vitamin E as the high-HLB surfactant component. An example of a preferred high-HLB surfactant from this class of surfactants is tocopheryl polyethylene glycol 1000 succinate ("TPGS"). TPGS is commercially available from Eastman Chemical Company as "Vitamin E TPGS", and has been used as a water-soluble Vitamin E supplement for oral ingestion. It is a waxy solid at room temperature and has melting point around 40° C. It has been found that the use of TPGS in corticosteroid compositions is particularly advantageous due to the ability of TPGS to solubilize corticosteroids and to form a stable micellar solution upon dilution in an aqueous phase, and also due to the neutral taste of TPGS when used in a corticosteroid composition that is administered either nasally or by inhalation. Consequently, an embodiment of the present invention that is particularly well suited for ease of manufacturing is one in which the corticosteroid compound is initially dissolved in TPGS to form a "concentrate" that is diluted with an aqueous phase to form the final corticosteroid composition. This composition is a micellar solution because the concentration of TPGS is far above the critical micellar concentration (CMC) of TPGS, which is about 0.02 wt. percent in water at 37° C. This embodiment is easy to manufacture, has a low level of excipients, and has a neutral taste for inhalation delivery.

Compositions designed for inhaled administration have a level of the high-HLB surfactant in the final, diluted corticosteroid composition from about 0.1 to about 20, preferably from about 0.25 to about 15, and more preferably from about 0.5 to about 5, percent by weight. Compositions designed for nasal administration have a level of the high-HLB surfactant in the final, diluted corticosteroid composition from about 1 to about 20, preferably from about 2.5 to about 15 and more preferably from about 5 to about 10, percent by weight.

The corticosteroids that are useful in the present invention generally include any steroid produced by the adrenocortex, including glucocorticoids and mineralocorticoids, and synthetic analogs and derivatives of naturally occurring corticosteroids having anti-inflammatory activity. Examples of corticosteroids that can be used in the compositions of the invention include aldosterone, beclomethasone, betamethasone, budesonide, cloprednol, cortisone, cortivazol, deoxyeortone, desonide, desoximetasone, dexamethasone, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluorometholone, flurandrenolone, fluticasone, halcinonide, hydrocortisone, icomethasone, meprednisone, methylprednisolone, paramethasone, prednisolone, prednisone, tixocortol, triamcinolone, and their respective pharmaceutically acceptable derivatives, such as beclomethasone diproprionate, dexamethasone 21-isonicotinate, fluticasone propionate, icomethasone enbutate, tixocortol 21-pivalate, and triamcinolone acetonide. Particularly preferred are compounds such as beclomethasone diproprionate, budesonide, flunisolide, fluticasone propionate, mometasone and triamcinolone acetonide.

The corticosteroid compound is present in the final, diluted corticosteroid composition designed for inhalation in an amount from about 5 μl to about 5 mg/ml, preferably from about 10 μg/ml to about 1 mg/ml, and more preferably from about 20 μg/ml to about 500 μg/ml. For example, the preferred drug concentration is between about 20 and 100 μg/ml for beclomethasone dipropionate, between about 30 and 150 μg/ml for triamcinolone acetonide, and between about 50 and 200 μg/ml for budesonide, depending on the volume to be administered. By following the preferred methods of the present invention, relatively high solubilities of the corticosteroid can be achieved in an aqueous-based composition. The solubility of the corticosteroid can be greater than about 50, preferably greater than about 75, and more preferably greater than about 100, in some cases greater than about 150 or about 200, μg/ml.

Similarly, the corticosteroid compound is present in the final, diluted corticosteroid composition designed for nasal administration in an amount from about 50 μg/ml to about 10 mg/ml, preferably from about 100 μg/ml to about 2 mg/ml, and more preferably from about 300 μg/ml to about 1 mg/ml. For example, the preferred drug concentration is between about 200 and 900 μg/ml for beclomethasone dipropionate, between about 250 μg/ml and 1 mg/ml for triamcinolone acetonide, and between about 400 μg/ml and 1.6 mg/ml for budesonide, depending on the volume to be administered.

The corticosteroid composition can also contain various excipients that improve the storage stability of the composition, but which do not significantly affect the overall efficacy of the composition in its freshly prepared state. Such excipients include buffers, osmotic (tonicity-adjusting) agents, low toxicity antifoaming agents, and preservatives.

Buffers are used in the present compositions to adjust the pH to a range of between about 4 and about 8, preferably between about 4.5 to about 7, and more preferably between about 5 and about 6.8. The buffer species may be any

pharmaceutically approved buffer providing the aforementioned pH ranges, such as citrate, phosphate, malate, etc.

The osmotic agent can be used in the compositions to enhance the overall comfort to the patient upon delivery of the corticosteroid composition. It is preferred to adjust the osmolality of the composition to about 280–300 mOsm/kg. Such agents include any low molecular weight water-soluble species pharmaceutically approved for pulmonary and nasal delivery such as sodium chloride and glucose.

Preservatives can be used to inhibit microbial growth in the compositions. The amount of preservative is generally that which is necessary to prevent microbial growth in the composition for a storage period of at least six months. Examples of pharmaceutically acceptable preservatives include the parabens, benzalkonium chloride, thimerosal, chlorobutanol, phenylethyl alcohol, benzyl alcohol, and potassium sorbate.

Corticosteroid compositions that contain the high-HLB surfactant can be prepared as follows. TPGS will be used as the representative high-HLB surfactant for illustrative purposes. First, the TPGS may be heated to a temperature of at least about 40° C., preferably at least about 45° C., and generally about 45–60° C. The appropriate quantity of the corticosteroid compound is then dissolved in the molten TPGS at the same temperature, thus forming the concentrated corticosteroid composition. To achieve the final, diluted corticosteroid composition, the molten concentrated corticosteroid composition is slowly added under continuous stirring to an aqueous phase. The aqueous phase is preferably water containing the additives necessary to adjust the pH and tonicity, and preservatives if the formulation is intended for multiple use. It is preferred that the aqueous phase be heated prior to the addition of the molten corticosteroid concentrate to aid in dispersion. Generally, the aqueous phase should be heated to about 55–85° C., more preferably from about 60–70° C.

It is preferred that the diluted corticosteroid composition be formulated by first dissolving the drug in the molten TPGS and then dispersing this concentrate in the aqueous phase. If the drug is added to a prediluted mixture of TPGS and aqueous phase, it may not be possible to achieve the final desired concentration of the drug in a dissolved state. To ensure that the drug is solubilized and stable in the diluted composition, it is preferred that the level of the drug in the concentrated composition be from about 1 to about 30 mg/ml, preferably from about 2 to about 20 mg/ml, and more 5 preferably from about 2 to about 10 mg/ml prior to dilution. The level of water in the concentrated corticosteroid composition should be below 5% by weight, preferably below 2% by weight, and more preferably below 1% by weight, and in general, it is advantageous not to add any water to the concentrated corticosteroid composition.

The aqueous phase, which is composed of water and optionally buffering, tonicity, and/or preservation additives, is present in the diluted corticosteroid compositions containing TPGS in an amount of at least about 70, preferably at least about 80, more preferably at least 90, and even more preferably at least about 95, percent by weight. The various other additives, such as buffers, tonicity adjusting agents, and preservatives, are preferably blended into the compositions as part of the aqueous phase, and the use of the term "aqueous phase" is intended to include such components, if used.

It has been found that the inclusion of any one of a group of cosolvents in these TPGS corticosteroid compositions can aid in the processing of the compositions and in the solubilizing of the drug. Preferred cosolvents include mono- and polyvalent alcohols, such as propylene glycol, ethanol, glycerol, glycofurol (available as Tetraglycol from Sigma), ethoxydiglycol (available as Transcutol from Gattefosse), and polyethylene glycol (PEG) having an average molecular weight between about 200 and 4000, preferably between 200 and 1000, more preferably PEG 400, and combinations thereof. The cosolvents can be present individually in the final, diluted corticosteroid compositions in concentrations from about 0.1 to about 20, preferably from about 0.25 to about 15, more preferably from about 0.5 to about 5, and even more preferably from about 0.5 to about 2.5, percent by weight. The total level of cosolvents combined in the final, diluted corticosteroid compositions is from about 0.1 to about 20, preferably from about 0.25 to about 15, more preferably from about 0.5 to about 10, and even more preferably from about 0.5 to about 5, percent by weight.

When preparing the corticosteroid compositions, the cosolvents can be added to the molten TPGS, to the TPGS/drug concentrate, or to the aqueous phase in which the TPGS/drug concentrate will be dispersed. Any way, stable diluted corticosteroid compositions can be produced with the drug in a dissolved state. If the cosolvents are blended with the molten TPGS prior to the addition of the drug, the temperature of this concentrate can then be reduced during the dissolution process. In general, the temperature of the TPGS/cosolvent mixture can be maintained below about 50° C., preferably below about 45° C., in order to dissolve the drug. In some cases, such as when a volatile cosolvent like ethanol is used, no heating is necessary to achieve dissolution. In addition, when the concentrated composition contains a cosolvent, it is not necessary to heat the aqueous phase used as the dilution medium to form the diluted corticosteroid composition.

Alternatively, the drug can be first dissolved in the cosolvent or blend of cosolvents at 20–50° C. and then that solution is blended with the molten TPGS to form the concentrated corticosteroid composition.

Other preferred high-HLB surfactants that can be used in place of, or in admixture with, ethoxylated derivatives of vitamin E are polyethylene glycol fatty acid esters. The fatty acid moiety preferably has from about 8 to about 18 carbon atoms. A preferred polyethylene glycol fatty acid high-HLB surfactant product is "Solutol HS-15," available from BASF Fine Chemicals. Solutol HS-15 is a mixture of polyethyleneglycol 660 12-hydroxystearate (70%) and polyethylene glycol (30%). It is a white paste at room temperature that becomes liquid at about 30° C. and has an HLB of about 15. Aqueous solutions of this surfactant, like those of TPGS, have a neutral taste. Similar preferred manufacturing processes and behavior regarding the dissolution of drugs, dilution methods, and the addition of cosolvents apply to Solutol HS-15 as those mentioned above for TPGS.

The corticosteroid compositions can contain other high-HLB surfactants, such as ethoxylated hydrogenated castor oil (Cremophor RH40 and RH60, available from BASF), tyloxapol, sorbitan esters such as the Tween series (from ICI Surfactants) or the Montanox series (from Seppic), etc. The corticosteroid compositions preferably contain either, or both, of the ethoxylated derivatives of vitamin E or the polyethylene glycol fatty acid esters as all or part of the high-HLB surfactant component, and in general the sum of these two types of surfactants will account for at least 50%, preferably at least 75%, and more preferably at least 90% by wt. of the high-HLB surfactant component.

Optionally, low HLB surfactants, having an HLB value below about 8, can also be used in the present invention.

Examples of such low HLB surfactants include phospholipids, such as phosphatidylethanolamine, phosphatidylcholine, and phosphatidylinositol; and medium-chain mono- and diglycerides, i.e., mono- and di-glycerides of C_8 to C_{12} fatty acids, and mixtures thereof. The low HLB surfactants can be used in general at levels from about 0.1 to about 3 percent by weight in the diluted composition.

Optionally, an oil can also be incorporated into the compositions. Examples of pharmaceutically acceptable oil compounds include triglycerides and propylene glycol diesters of C_8 to C_{12} fatty acids such as the Captex series available from Abitec. Oils can be used in general in levels from about 1 to about 30 percent by weight in the concentrated compositions and from about 0.1 to about 3 percent by weight in the diluted composition.

It is necessary to add the drug to the compositions containing high-HLB and low HLB surfactants, and/or cosolvents, and/or the oil compounds, to form the concentrated corticosteroid compostion prior to dilution with the aqueous phase.

The diluted corticosteroid compositions using high-HLB surfactants such as TPGS or Solutol HS-15 to solubilize the drug are believed to be micellar compositions. This belief is based on the fact that the critical micelle concentration for both TPGS and Solutol HS-15 is about 0.02% by weight at 37° C., which is below their concentration in the diluted corticosteroid compositions. If an oil component is present with or without a low HLB surfactant, an oil-in-water (o/w) microemulsion may be formed as the diluted corticosteroid composition.

The aforementioned diluted compositions can be administered to the body in the form of an aerosol. For administration to the respiratory tract, particularly the lungs, a nebulizer is used to produce appropriately sized droplets. Typically, the particle size of the droplet produced by a nebulizer for inhalation is in the range between about 0.5 to about 5 microns. If it is desired that the droplets reach the lower regions of the respiratory tract, i.e., the alveoli and terminal bronchi, the preferred particle size range is between about 0.5 and about 2.5 microns. If it is desired that the droplets reach the upper respiratory tract, the preferred particle size range is between 2.5 microns and 5 microns. The nebulizer operates by directing pressurized air to fluidize the droplets of the diluted corticosteroid composition, which resultant aerosol is directed through a nozzle and subsequently through a baffle system that removes larger particles.

For the treatment of bronchial constriction, the diluted corticosteroid composition is prepared as described above. The corticosteroid for such treatment is preferably either beclomethasone dipropionate, betamethasone, budesonide, dexamethasone, flunisolide, fluticasone propionate, or triamcinolone acetonide, and is formulated in the concentrations set forth above. The daily dose of the corticosteroid is generally about 0.4 to 2 mg, depending on the drug and the disease, in accordance with the Physician's Desk Reference.

EXAMPLES

Various embodiments of the present invention are illustrated by the following examples, which should not be intended to limit the scope of the invention. The compositions of Examples 1, 2, 3, and 5 are suitable for inhalation via nebulization and the composition of Example 4 is suitable for nasal administration.

Example 1

The glucocorticoid beclomethasone dipropionate monohydrate was dissolved in premelted (50° C.) TPGS at concentrations of 2.8 and 6.3 mg per gram. These concentrates were kept at 50° C. during the entire solubilization process, which was about 15 min. While in this molten form, the concentrates were diluted at various volume ratios from 1:10 to 1:100 in various aqueous solutions such as hot (80° C.) deionized water, saline, malate buffer, citrate buffer, phosphate buffer, and 5% solutions of propylene glycol, PEG 200, or PEG 400 in any of the above. These diluted compositions were blended until any gel that may have formed when the TPGS concentrate came into contact with the aqueous phase was completely dispersed. Transparent, physically stable, diluted corticosteroid compositions without any precipitates were obtained containing about 28 to 420 μg/ml beclomethasone dipropionate. The diluted corticosteroid compositions were sterilized by passing them through a 0.22 micron sterile filter.

Example 2

Beclomethasone dipropionate monohydrate (4.2 mg) was dissolved in 995.8 mg of a binary liquid mixture of TPGS and ethanol (1:1 weight ratio) by briefly mixing at room temperature to form a concentrated corticosteroid composition. The concentrate was diluted 1:100 by volume in solutions of 5 wt.% PEG 400 in either deionized water, saline, or 20 mM malate, citrate, or phosphate buffer, by mixing for several minutes at room temperature. The resulting optically transparent, diluted corticosteroid compositions contained about 42 μg beclomethasone dipropionate per ml. The diluted corticosteroid compositions were sterilized by passing them through a 0.22 micron sterile filter.

The same concentrated corticosteroid composition was also diluted 1:50 by volume in the above-mentioned aqueous phases, and resulted in final formulations containing about 84 μg beclomethasone dipropionate per ml. These diluted formulations were physically and chemically stable for over a year at 5° C., 25° C./60% RH and 40° C./75% RH.

Example 3

Several corticosteroids—beclomethasone dipropionate, budesonide, and triamcinolone acetonide—were dissolved in binary mixtures of TPGS and a cosolvent selected from the group of ethanol, propylene glycol, PEG 200 and PEG 400. The weight ratio of TPGS to cosolvent was 1:1, and the resulting drug concentrations were between 1.4 and 4.0 mg/gram. It was necessary to heat the TPGS/propylene glycol and the TPGS/PEG mixtures to approximately 45° C. for several minutes in order to dissolve the drugs, but dissolution could be achieved in the TPGS/ethanol mixture at room temperature. The concentrates were diluted 1:50 by volume in an aqueous phase (5% wt. PEG 400 in deionized water) resulting in clear solutions containing from 28 μg to 80 μg per mL. The diluted corticosteroid compositions were sterilized by passing them through a 0.22 micron sterile filter.

Example 4

The composition of this example is suitable for nasal administration. Beclomethasone dipropionate monohydrate (2.8 mg) was dissolved in 997.2 mg of a 2:1 w/w mixture of PEG 200 and TPGS and then diluted (1:6.65 by volume) with deionized water. The final transparent solution contained 420 μg of beclomethasone dipropionate per mL of solution. The composition of the formulation is given below. The tonicity can be adjusted to about 300 mOsm/kg by the addition of glucose or sodium chloride.

Component	Weight Percent Concentrate Mixture	Wt/Vol. Percent After 1:6.65 Dilution
TPGS	33.24	5
PBG 200	66.48	10
Beclomethasone dipropionate	0.28	0.042
Deionized water	—	q.s.

The diluted corticosteroid compositions were sterilized by passing them through a 0.22 micron sterile filter.

Example 5

In order to assess the stability profiles of some of the corticosteroid compositions described in this invention, four formulations were made with the weight compositions given in the following table.

Component	Form. 1	Form. 2	Form. 3	Form. 4
Beclomethasone dipropionate	42 μg/g	42 μg/g	42 μg/g	42 μμg/g
TPGS	1%	1%	0.5%	0.5%
Polyethylene glycol 400	—	1%	5%	5%
Ethyl Alcohol (190 Proof)	—	—	0.5%	0.5%
Deionized Water	q.s.	q.s.	q.s	—
0.9% NaCl Solution	—	—	—	q.s.

Formulations were stored in glass vials and blow-molded polyethylene ampules for the duration of the study. Various tests were used to assess the physical and chemical stability of the corticosteroid compositions given above.

Size and distribution of the dispersed material droplets in the aqueous solution of the above compositions were determined using a quasi-elastic light scattering technique. The experimental equipment consisted of a BI-200SM Goniometer and BI9000AT Digital Correlator from Brookhaven Instrument Corporation, and a Thorn EMI Electron tube for detection powered by a high voltage power supply, delivering 2000 volts, from Bertan Associates. A helium-neon laser from Spectra Physics was the light source, with a wavelength of 632.8 nm. The droplet size of the dispersed phase in all formulations before nebulization was about 10 nm, and remained constant for the duration of the study.

The MMAD and the corresponding geometric standard deviation (GSD) of the nebulized corticosteroid compositions were determined at time zero of the study. Saline was used as a reference. The experiments were done using a system consisting of a Proneb compressor and a Pari LC Plus Reusable Nebulizer (Pari Respiratory Equipment, Inc., Richmond, Va.) equipped with an adapted mouthpiece, connected in series with an Andersen cascade impactor (Andersen Airsampler Inc., Atlanta, Ga.). A vacuum pump was connected to the outlet of the cascade impactor, and between them was an air flow controller which indicated a flow of about 28.3 L/min. A cascade impactor is a mechanical model of human lung, containing seven stages and a filter before the outlet, which represent increasing depths of penetration. The amount of excipients deposited on each plate was determined by the increase in the plate dry weight. Analogous results were obtained when determining the MMAD from the drug mass on each plate. This showed that the drug travels in same manner as the excipients.

Formulation	MMAD (μm)	% GSD
1	2.939	2.81
2	2.294	2.46
3	2.795	2.48
4	2.165	2.42
Saline	2.216	2.16

Analysis for the corticosteroid content and degradation products in the above compositions was performed by HPLC. A Shimadzu LC 10A was used with a Supelcosil LC-318 column and UV/VIS detector monitoring absorbance at a wavelength of 254 nm. The isocratic method used 60% acetonitrile in deionized water at a flow rate of about 1.5 mL/min for 15 min. Visual examinations of the corticosteroid compositions under crossed polarized light films and by the naked eye were made on a weekly basis. These examinations were done in order to observe over time whether there was any phase separation, drug precipitate, turbidity or change in color. Results of the stability study at 40° C./75% RH after 12 weeks are shown below. From these data it can be concluded that the tested formulations are physically stable, meaning that there was no phase separation or precipitation of the drug under stressed conditions. No degradation of the corticosteroid was observed. Similar results were obtained from samples which were stored at 5° C. and 25° C.

Formulation	Drug content, t = 0, μg/mL	Drug content, t = 12 wk μg/mL glass vials	LDPE ampules
1	43.09	45.08 (104.6)	45.49 (105.6)
2	42.55	43.80 (102.9)	44.32 (104.2)
3	41.96	42.91 (102.3)	43.06 (102.6)
4	41.31	41.55 (100.6)	41.26 (99.9)

What is claimed is:

1. An aerosolized composition for administering a therapeutic dose of a corticosteroid to respiratory tract, consisting essentially of:

(a) from 5 μg/mL to about 5 mg/mL of a dissolved corticosteroid;

(b) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component containing one or more surfactants having an HLB of greater than 10, wherein The high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and

(c) at least about 70 weight percent aqueous phase.

2. The composition of claim 1 wherein the corticosteroid comprises beclomethasone dipropionate.

3. The composition of claim 1 wherein the corticosteroid comprises budesonide.

4. The composition of claim 1 wherein the corticosteroid comprises triamcinolone acetonide.

5. The composition of claim 1 wherein the corticosteroid comprises fluticasone propionate.

6. The composition of claim 1 wherein the corticosteroid comprises flunisolide.

7. The composition of claim 1 wherein the high-HLB surfactant component comprises at least 50% by weight tocopheryl polyethylene glycol 1000 succinate.

8. The composition of claim 1 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

9. The composition of claim 1 wherein the ethoxylated derivative of vitamin E comprises at least 90% by weight of the high-HLB surfactant component.

10. The composition of claim 1 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

11. The composition of claim 1 wherein the high-HLB surfactant component comprises at least 90% by weight tocopheryl polyethylene glycol 1000 succinate.

12. An aerosolized composition for administering a therapeutic dose of a corticosteroid to respiratory tract, composing:

(a) from 5 μg/mL to about 5 mg/mL of a dissolve corticosteroid;

(b) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component containing one or more surfactants having an HLB of greater than 10, wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and

(c) at least about 70 weight percent aqueous phase.

13. The composition of claim 12 wherein the high-HLB surfactant component comprises at least 75 percent by weight of an ethoxylated derivative of vitamin E.

14. The composition of claim 12 wherein the high-HLB surfactant component comprises at least 90 percent by weight of an ethoxylated derivative of vitamin E.

15. The composition of claim 12 further comprising from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable cosolvent comprising propylene glycol, polyethylene glycol having a molecular weight between about 200 and 4000, glycerol, ethoxydiglycol, glycofurol, and ethanol, or a combination thereof.

16. The composition of claim 12 further comprising from about 0.1 to about 3 percent by weight of a low HLB surfactant having an HLB below about 8.

17. The composition of claim 12 further comprising from about 0.1 to about 3 percent by weight of an oil.

18. The composition of claim 12 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

19. The composition of claim 12 wherein the high-HLB surfactant component comprises at least 90% by weight tocopheryl polyethylene glycol 1000 succinate.

20. A method for administering a therapeutic dosage of an aerosolized corticosteroid to respiratory tract of a patient in need thereof, comprising:

(a) providing a corticosteroid composition comprising:

(1) from 5 μg/mL to about 5 mg/mL of a dissolved corticosteroid;

(2) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component containing one or more surfactants having an HLB of greater than 10, wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and

(3) at least about 70 weight percent aqueous phase;

(b) aerosolizing the corticosteroid composition; and

(c) administering a therapeutically effective dosage of the aerosolized composition to said patient by inhalation.

21. The method of claim 20 wherein the corticosteroid composition consists essentially of said corticosteroid, said aqueous phase, and said high-HLB surfactant.

22. The method of claim 20 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

23. The method of claim 20 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

24. A method for administering a therapeutic dosage of an aerosolized corticosteroid composition to the nasal passage of a patient in need thereof, comprising:

(a) providing a corticosteroid composition comprising:

(1) from 5 μg/mL to about 5 mg/L of a dissolved corticosteroid;

(2) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component containing one or more surfactants, having an HLB of greater than 10, wherein high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and

(3) at least about 70 weight percent aqueous phase,

(b) administering a therapeutically effective dosage of the corticosteroid composition by nasal inhalation to said patient.

25. The method of claim 24 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

26. The method of claim 24 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

27. A method of preparing a diluted corticosteroid composition containing a dissolved corticosteroid, composing:

(a) dissolving a corticosteroid compound into a molten pharmaceutically acceptable high-HLB surfactant component comprising one or more surfactants having an HLB greater than 10, and wherein the high-HLB surfactant component comprises at least 50 percent by weight of an etioxylated derivative of vitamin E;

(b) subsequently blending The molten high-HLB surfactant component containing the dissolved corticosteroid with an aqueous phase,

wherein the aqueous phase is present in an amount of at least about 70 weight percent, and the high-HLB surfactant component is present in an amount of from about 0.1 to about 20 weight percent, of the diluted corticosteroid composition.

28. The method of claim 27 wherein the ethoxylated derivative of vitamin E comprises at least 75% by weight of the high-HLB surfactant component.

29. The method of claim 27 wherein the high-HLB surfactant component comprises at least 75% by weight tocopheryl polyethylene glycol 1000 succinate.

* * * * *

Exhibit I

Terminal Disclaimer To Obviate A Double Patenting Rejection Over A Prior Patent	Docket No. P24800-A USA

In Re Application Of: **Zahir Saidi and Boris Klyashchitsky**

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
10/019,100	August 21, 2003	L. Soroush	23307	1617	8648

Invention: **AQUEOUS COMPOSITIONS CONTAINING CORTICOSTEROIDS FOR NASAL AND PULMONEY DELIVERY**

Owner of Record: **Elan Corporation, plc**

COMMISSIONER FOR PATENTS:

The above-identified owner of record of a 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. 6,241,969 . The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors and/or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

Signature Dated: **November 29, 2007**

Jonathan M. Dermott
Typed or Printed Name

☒ Terminal disclaimer fee under 37 C.F.R. 1.20(d) included.
☒ PTO suggested wording for terminal disclaimer was unchanged.
☐ Certification under 37 C.F.R. 3.73(b) is required if terminal disclaimer is signed by the assignee.

Exhibit J

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,100	08/21/2003	Zahir Saidi	P24,800-A USA	8648

7590 04/15/2009

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EXAMINER	
SOROUSH, LAYLA	
ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
04/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/019,100	SAIDI ET AL.	
	Examiner	Art Unit	
	LAYLA SOROUSH	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-10 and 13-27* is/are pending in the application.

4a) Of the above claim(s) *5,7-9 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,10,13-17 and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed January 27, 2009 presents remarks and arguments submitted to the office action mailed October 28, 2008 is acknowledged.

Applicant's arguments over the 35 U.S.C. 103(a) rejection of claims 1, 6, 10, 13-17 and 22-27 over Sonne (US Pat No. 6,193,985– previously presented) is not persuasive. Therefore, the rejection of record is maintained.

Applicant makes no arguments regarding the ODP rejection made over U.S. Patent No. 6241969. Therefore, the rejection of record is maintained.

The rejections are restated below for Applicant's convenience.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 10, 13-17 and 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sonne (US Pat No. 6,193,985– previously presented).

The invention reads on a composition consisting of: (a) from 5 ug/mL to about 5 mg/mL of a corticosteroid in dissolved form; (b) from about 0.1 to 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants present in the high HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E, wherein said ethoxylated derivative

of vitamin E is the sole vitamin E component of the composition; and (c) at least about 70 weight percent aqueous phase.

Sonne discloses an oil in water emulsion of budesonide as nose drop or nasal spray, comprising in the oily phase 0.025 grams of budesonide, 5 grams of vitamin e TPGS and 12.5 grams alpha-tocopherol – (viscous oil (surfactant)) (see col 3 line 18, col 11 Example 15). The limitation of the composition having at least about 70 weight percent of aqueous phase is met by the teachings of the water phase in the prior art (col 11 Example 15). Additionally, Sonne et al. teaches "Generally speaking compositions of the invention may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative solvent. The emulsion used in compositions of the invention may contain 1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w) (Col 5 lines 55-61)." Sonne teaches "the formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired. Thus for example, the following co-solvents may be added: Vegetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin, (col 6 lines 47-59)" meeting the limitation of claims 15 and 17. Further, Sonne teaches "the tocopherol derivative emulsifier of the invention may be used alone or in conjunction with other known emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers. It has furthermore surprisingly been shown that various other

solvents may be used in the emulsion system described above, without compromising the stability of the emulsion (col 4 lines 50-56)."

Sonne fails to exemplify a composition "wherein said ethoxylated derivative of vitamin E is the sole vitamin E component of the composition," or comprising a high-HLB surfactant component of at least 50%, 75%, 90% by weight tocopheryl polyethylene glycol 1000 succinate. Further, Sonne does not exemplify a composition containing from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable cosolvent comprising propylene glycol, polyethylene glycol having a molecular weight between about 200 and 4000, glycerol, ethoxydiglycol, glycofurol, and ethanol, or a combination thereof, 0.1 to about 3 percent by weight of phospholipids, nor 0.1 to about 3 percent by weight of an oil.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the composition by substituting the alpha-tocopherol of Example 15 with a vitamin e-TPGS and incorporating additional ingredients such as oils or alcohols inclusive of ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin, or emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers. The motivation to make such an incorporation is because Sonne teaches (1) it has been surprisingly found "that tocopherol derivatives, particularly certain esters, may themselves form efficient, non-irritating emulsifiers to enable stable emulsions to be formed, even where high lipid levels are involved eg. about 50-70%. Particular mention may be made in this regard of Vitamin E TPGS which is a water soluble derivative of Vitamin E and consists of .alpha.-

tocopherol, which is esterified with succinic acid, the other acidic group of the latter being esterified with polyethylene glycol 1000. Vitamin E TPGS is an almost odourless waxy amphiphilic substance with a molecular weight about 1513 (col 4, lines 27-35);" (2) the formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired. Thus for example, the following co-solvents may be added: Vegetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or triacetin and (3) the tocopherol derivative emulsifier of the invention may be used alone or in conjunction with other known emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetearyl glucoside or poloxamers. It has furthermore surprisingly been shown that various other solvents may be used in the emulsion system described above, without compromising the stability of the emulsion. Hence, the skilled artisan would have had reasonable expectation of successfully producing a composition that is non-irritating with optimized bioadhesion, sprayability, viscosity, without compromising the stability of the emulsion.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the dose range of the Sonne composition by routine experimentation (see 2144.05 11). The motivation to optimize the dose range of the Sonne 's final formulation is because one would have had a reasonable expectation of success in achieving the safest clinical outcome.

The composition "suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract" is an intended use and does not receive patentable weight in a composition claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 10, 12-17, and 22-27 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6241969 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the invention herein is directed to a composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting essentially of: (a)from about 5 ug/ml to about 5 mg/ml of a

corticosteroid in dissolved form, (b)from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants is greater than about 10, and (c) at least about 70 weight percent aqueous phase whereas, the Patent is directed to an aerosolized composition for administering a therapeutic dose of a corticosteroid to respiratory tract, consisting essentially of: (a) from 5 ug/mL to about 5 mg/mL of a dissolved corticosteroid; (b) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component containing one or more surfactants having an HLB of greater than 10, wherein The high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E; and (c) at least about 70 weight percent aqueous phase.

Response to Arguments

Applicant's arguments filed January 27, 2009 have been fully considered but are not persuasive.

Applicant argues the alpha-tocopherol is the most crucial element of the Sonne reference and that Sonne does not provide any motivation to remove alpha-tocopherol from his composition.

Examiner states that Sonne clearly discloses "the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions (see abstract)." It is respectfully stated that the 35 U.S.C. 103(a) rejection above is not a anticipatory rejection. Though, the reference does not exemplify the sole use of vitamin E TPGS in a composition, one of ordinary skill in the art would have been readily

motivated to utilize a tocopherol derivative in order to produce an efficient, non-irritating, and stable emulsion because Sonne teaches the use of a tocopherol or a derivative thereof.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The arguments are not persuasive and the rejection is made **FINAL**.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Soroush whose telephone number is (571)272-5008. The examiner can normally be reached on Monday through Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617

Exhibit K

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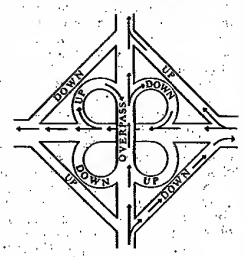
— **in clover** or **in the clover** : in prosperity or in pleasant circumstances

¹clo·ver·leaf \-ˌlēf\ *adj* (1917) : resembling a clover leaf in shape

²cloverleaf *n, pl* **-leafs** \-ˌlēfs\ *or* **-leaves** \-ˌlēvz\ (1931) : an interchange between two major highways that allows traffic to change from one to the other without requiring any left turns or crossings and that from above resembles a four-leaf clover



cloverleaf

Clo·vis \'klō-vəs\ *adj* [*Clovis*, New Mexico] (1956) : of or relating to a widely distributed prehistoric culture of No. America characterized by leaf-shaped flint projectile points having fluted sides

¹clown \'klau̇n\ *n* [prob. of LG origin; akin to Fris *klönne* clumsy fellow, OE *clyne* lump of metal] (1563) **1** : FARMER, COUNTRYMAN **2** : a rude ill-bred person : BOOR **3 a** : a fool, jester, or comedian in an entertainment (as a play); *specif* : a grotesquely dressed comedy performer in a circus **b** : a person who habitually plays the buffoon **c** : JOKER 1b

²clown *vi* (1599) : to act as or like a clown

clown·ery \'klau̇-nə-rē\ *n, pl* **-er·ies** (1589) : clownish behavior or an instance of clownishness : BUFFOONERY

clown·ish \'klau̇-nish\ *adj* (ca. 1570) : resembling or befitting a clown (as in ignorance and lack of sophistication) *syn* see BOORISH — **clown·ish·ly** *adv* — **clown·ish·ness** *n*

clox·a·cil·lin \ˌkläk-sə-'si-lən\ *n* [*chlor-* + *oxacillin*] (1963) : a semisynthetic oral penicillin $C_{19}H_{17}ClN_3NaO_5S$ effective esp. against staphylococci which secrete penicillinase

cloy \'klȯi\ *vb* [alter. of ME *acloien* to lame, fr. MF *encloer* to drive in a nail, fr. ML *inclovare*, fr. L in + *clavus* nail] *vt* (1528) : to surfeit with an excess usu. of something orig. pleasing ~ *vi* : to cause surfeit *syn* see SATIATE

cloy·ing \'klȯi-iŋ, 'klȯiŋ\ *adj* (1594) : disgusting or distasteful by reason of excess ⟨~ sweetness⟩; *also* : excessively sweet or sentimental ⟨a ~ romantic comedy⟩ — **cloy·ing·ly** *adv*

cloze \'klōz\ *adj* [by shortening & alter. fr. *closure*] (1953) : of, relating to, or being a test of reading comprehension that involves having the person being tested supply words which have been systematically deleted from a text

¹club \'kləb\ *n, often attrib* [ME *clubbe*, fr. ON *klubba*; akin to OHG *kolbo* club] (13c) **1 a** : a heavy usu. tapering staff esp. of wood wielded as a weapon **b** : a stick or bat used to hit a ball in any of various games **c** : something resembling a club **2 a** : a playing card marked with a stylized figure of a black clover **b** *pl but sing* or *pl in constr* : the suit comprising cards marked with clubs **3 a** : an association of persons for some common object usu. jointly supported and meeting periodically; *also* : a group identified by some common characteristic ⟨nations in the nuclear ~⟩ **b** : the meeting place of a club **c** : an association of persons participating in a plan by which they agree to make regular payments or purchases in order to secure some advantage **d** : NIGHTCLUB **e** : an athletic association or team — **club·bish** \'klə-bish\ *adj*

²club *vb* **clubbed; club·bing** *vt* (1593) **1 a** : to beat or strike with or as if with a club **b** : to gather into a club-shaped mass ⟨*clubbed* her hair⟩ **2 a** : to unite or combine for a common cause **b** : to contribute to a common fund ~ *vi* **1** : to form a club : COMBINE **2** : to pay a share of a common expense

club·ba·ble *also* **club·able** \'klə-bə-bəl\ *adj* (1783) : SOCIABLE

clubbed \'kləbd\ *adj* (14c) : shaped like a club ⟨~ antennae⟩

club·ber \'klə-bər\ *n* (1633) : a member of a club

club·by \'klə-bē\ *adj* **club·bi·er; -est** (1859) : characteristic of a club or club members: as **a** : displaying friendliness esp. to other members of the same social group : SOCIABLE **b** : open only to qualified or approved persons : SELECT, ELITE — **club·bi·ness** *n*

club car *n* (1886) : a railroad passenger car with facilities for serving refreshments and drinks — called also *bar car, lounge car*

club chair *n* (1919) : a deep low thickly upholstered easy chair often with rather low back and heavy sides and arms

club cheese *n* (1916) : a process cheese made by grinding cheddar and other cheeses usu. with added condiments and seasoning

club·foot \'klə-ˌfu̇t\ *n* (1538) : a misshapen foot twisted out of position from birth; *also* : this deformity — **club·foot·ed** \-ˌfu̇-təd\ *adj*

club fungus *n* (1899) : any of a family (Clavariaceae) of basidiomycetes with a simple or branched often club-shaped sporophore

club·house \'klə-ˌhau̇s\ *n* (1818) **1** : a house occupied by a club or used for club activities **2** : locker rooms used by an athletic team

club·man \'klə-mən, -ˌman\ *n* (1851) : a usu. wealthy man given to club life

club moss *n* (1597) : any of an order (Lycopodiales) of primitive vascular plants (as ground pine) often with the sporangia borne in club-shaped strobili

club·root \'klə-ˌrüt, -ˌru̇t\ *n* (1846) : a disease of cruciferous plants and esp. of cabbage caused by a slime mold (*Plasmodiophora brassicae*) producing swellings of the roots

club sandwich *n* (1903) : a sandwich of three slices of bread with two layers of meat (as turkey) and lettuce, tomato, and mayonnaise

club soda *n* (1942) : SODA WATER 2a

club steak *n* (1915) : a small steak cut from the end of the short loin — see BEEF illustration

¹cluck \'klək\ *vb* [imit.] *vi* (15c) **1** : to make a cluck **2** : to make a clicking sound with the tongue **3** : to express interest or concern ⟨critics ~*ed* over the new developments⟩ ~ *vt* **1** : to call with a cluck **2** : to express with interest or concern

²cluck *n* (1703) **1** : the characteristic sound made by a hen esp. in calling her chicks **2** : a stupid or naive person

¹clue \'klü\ *n* [alter. of *clew*] (1596) : something that guides through an intricate procedure or maze of difficulties; *specif* : a piece of evidence that leads one toward the solution of a problem

²clue *vt* **clued; clue·ing** *or* **clu·ing** (1663) **1** : to provide with a clue **2** : to give reliable information to ⟨~ me in on how it happened⟩

clue·less \'klü-ləs\ *adj* (1862) **1** : providing no clue **2** : completely or hopelessly bewildered, unaware, ignorant, or foolish

clum·ber spaniel \'kləm-bər-\ *n, often cap C* [*Clumber*, estate in Nottinghamshire, England] (1883) : any of a breed of large massive heavy-set spaniels with a dense silky largely white coat

¹clump \'kləmp\ *n* [prob. fr. LG *klump*] (ca. 1586) **1** : a group of things clustered together ⟨a ~ of bushes⟩ **2** : a compact mass **3** : a heavy tramping sound — **clumpy** \'kləm-pē\ *adj*

²clump *vi* (1665) **1** : to walk or move clumsily and noisily **2** : to form clumps ~ *vt* : to arrange in or cause to form clumps ⟨the serum ~s the bacteria⟩

clum·sy \'kləm-zē\ *adj* **clum·si·er; -est** [prob. fr. obs. E *clumse* benumbed with cold] (ca. 1598) **1 a** : lacking dexterity, nimbleness, or grace ⟨~ fingers⟩ **b** : lacking tact or subtlety ⟨a ~ joke⟩ **2** : awkward or inefficient in use or construction : UNWIELDY *syn* see AWKWARD — **clum·si·ly** \-zə-lē\ *adv* — **clum·si·ness** \-zē-nəs\ *n*

clung *past and past part of* CLING

¹clunk \'kləŋk\ *vb* [imit.] *vi* (ca. 1796) **1** : to make a clunk **2** : to hit something with a clunk ~ *vt* : to strike or hit with a clunk

²clunk *n* (1823) **1** : a blow or the sound of a blow : THUMP **2** : a dull or stupid person

clunk·er \'kləŋ-kər\ *n* (1943) **1** : an old or badly working piece of machinery; *esp* : a dilapidated automobile **2** : someone or something notably unsuccessful

clunky \'kləŋ-kē\ *adj* **clunk·i·er; -est** (1968) : clumsy in style, form, or execution ⟨a ~ thriller⟩ ⟨~ earrings⟩

clu·pe·id \'klü-pē-əd\ *n* [ultim. fr. L *clupeo*, a small river fish] (1880) : any of a large family (Clupeidae) of soft-finned bony fishes (as herrings) that have a laterally compressed body and a forked tail and usu. occur in schools — **clupeid** *adj*

¹clus·ter \'kləs-tər\ *n* [ME, fr. OE *clyster*; akin to OE *clott* clot] (bef. 12c) **1** : a number of similar individuals that occur together; as **a** : two or more consecutive consonants or vowels in a segment of speech **b** : a group of buildings and esp. houses built close together on a sizable tract in order to preserve open spaces larger than the individual yard for common recreation **c** : an aggregation of stars or galaxies that appear close together in the sky and are gravitationally associated — **clus·tery** \-t(ə-)rē\ *adj*

²cluster *vb* **clus·tered; clus·ter·ing** \-t(ə-)riŋ\ *vt* (14c) **1** : to collect into a cluster ⟨~ the tents together⟩ **2** : to furnish with clusters ~ *vi* : to grow, assemble, or occur in a cluster

cluster analysis *n* (1948) : a statistical classification technique for discovering whether the individuals of a population fall into different groups by making quantitative comparisons of multiple characteristics

cluster bomb *n* (1967) : an aircraft-dropped canister of small fragmentation bombs

cluster headache *n* (1953) : a headache that is characterized by severe pain in the eye or temple and tends to recur in a series of attacks

¹clutch \'klәch\ *vb* [ME *clucchen*, fr. OE *clyccan*] *vt* (bef. 12c) **1** : to grasp or hold with or as if with the hand or claws usu. strongly, tightly, or suddenly **2** *obs* : CLENCH ~ *vi* **1** : to seek to grasp and hold **2** : to operate an automobile clutch *syn* see TAKE

²clutch *n* (13c) **1 a** : the claws or a hand in the act of grasping or seizing firmly **b** : an often cruel or unrelenting control, power, or possession ⟨the fell ~ of circumstance —W. E. Henley⟩ **c** : the act of grasping, holding, or restraining **2 a** : a coupling used to connect and disconnect a driving and a driven part of a mechanism **b** : a lever (as a pedal) operating such a clutch **3** : a tight or critical situation : PINCH ⟨come through in the ~⟩ **4** : CLUTCH BAG

³clutch *adj* (1944) **1** : made or done in a crucial situation ⟨a ~ hit⟩ **2** : successful in a crucial situation ⟨a ~ pitcher⟩

⁴clutch *n* [alter. of dial. E *cletch* hatching, brood] (1721) **1** : a nest of eggs or a brood of chicks **2** : GROUP, BUNCH

clutch bag *n* (1949) : a woman's small usu. strapless handbag

¹clut·ter \'klə-tər\ *vb* [ME *clotteren* to clot, fr. *clot*] *vt* (1556) *chiefly dial* : to run in disorder ~ *vt* : to fill or cover with scattered or disordered things that impede movement or reduce effectiveness — often used with *up*

²clutter *n* (1649) **1 a** : a crowded or confused mass or collection **b** : things that clutter a place **2** : interfering radar echoes caused by reflection from objects (as on the ground) other than the target **3** *chiefly dial* : DISTURBANCE, HUBBUB

Clyde \'klīd\ *n* (1894) : CLYDESDALE

Clydes·dale \'klīdz-ˌdāl\ *n* (1786) : a heavy draft horse with feathering on the legs of a breed orig. from Clydesdale, Scotland

clyp·e·us \'klī-pē-əs\ *n, pl* **clyp·ei** \-pē-ˌī, -pē-ˌē\ [NL, fr. L, round shield] (1834) : a plate on the anterior median aspect of an insect's head

clys·ter \'klis-tər\ *n* [ME, fr. MF or L; MF *clistere*, fr. L *clyster*, fr. Gk *klystēr*, fr. *klyzein* to wash out; akin to W *clir* pure, OE *hlūtor* clean] (14c) : ENEMA

Cly·tem·nes·tra \ˌklī-təm-'nes-trə\ *n* [L, fr. Gk *Klytaimnēstra*] : the wife and murderess of Agamemnon

cni·dar·i·an \nī-'dar-ē-ən, -'der-\ *n* [ultim. fr. NL *cnida* nematocyst, fr. Gk *knidē* nettle] (ca. 1909) : COELENTERATE — **cnidarian** *adj*

co- *prefix* [ME, fr. L, fr. *com-*; akin to OE *ge-*, perfective and collective prefix, OIr *com-* with] **1** : with : together : joint : jointly ⟨*co*exist⟩ ⟨*co*heir⟩ **2** : in or to the same degree ⟨*co*extensive⟩ **3 a** : one that is associated in an action with another : fellow : partner ⟨*co*author⟩ ⟨*co*worker⟩ **b** : having a usu. lesser share in duty or responsibility : alternate : deputy ⟨*co*pilot⟩ **4** : of, relating to, or constituting the complement of an angle ⟨cosine⟩ ⟨*co*declination⟩

co·act	co·chair	co·cre·ator
co·ac·tive	co·chair·man	co·cul·ti·vate
co·ac·tor	co·chair·per·son	co·cul·ti·va·tion
co·ad·min·is·tra·tion	co·chair·wom·an	co·cul·ture
co·an·chor	co·cham·pi·on	co·cu·ra·tor
co·au·thor	co·com·pos·er	co·de·fen·dant
co·au·thor·ship	co·con·spir·a·tor	co·de·sign
co·cap·tain	co·coun·sel	co·de·vel·op
co·cat·a·lyst	co·cre·ate	co·de·vel·op·er

Exhibit L

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(54) Title: AQUEOUS COMPOSITIONS CONTAINING CORTICOSTEROIDS FOR NASAL AND PULMONARY DELIVERY

(57) Abstract

The present invention provides compositions containing corticosteroid compounds as active agents for the treatment of ailments and diseases of the respiratory tract, particularly the lungs, by way of nasal and pulmonary administration. The corticosteroid compounds are present in a dissolved state in the compositions. The compositions can be formulated in a concentrated, essentially non-aqueous form for storage or in a diluted, aqueous-based form for ready delivery. In a preferred embodiment, the corticosteroid composition contains an ethoxylated derivative of vitamin E and/or a polyethylene glycol fatty acid ester as the high-HLB surfactant present in the formulation. The compositions are ideally suited for inhaled delivery with a nebulizer or for nasal delivery.

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AQUEOUS COMPOSITIONS CONTAINING CORTICOSTEROIDS FOR NASAL AND PULMONARY DELIVERY

FIELD OF THE INVENTION

The present invention relates to pulmonary drug delivery compositions useful for the inhaled administration of corticosteroid compounds and the method of their administration. The delivery compositions are useful for the treatment of ailments and diseases of the lungs. Similar corticosteroid compositions may be used for nasal delivery.

BACKGROUND OF THE INVENTION

Delivery of therapeutic compounds directly to affected lung tissues has several advantages. The drug reaches the target tissue without first entering the systemic circulation and being subjected to dilution by the blood, binding to blood components, or metabolism by the liver and excretion by the kidneys. A high local concentration of drug can be achieved in the lungs while the systemic concentration is kept below that likely to cause adverse side effects. In addition, the apical side of the lung tissue – the side exposed directly to inspired air – can be treated with compounds that might not readily cross the endothelium or epithelium, which form barriers between the apical surface and the blood plasma. Similar considerations apply to the tissues lining the nasal passages and sinus cavities.

Several means have been developed to deliver compounds directly to the passages of the lung or nose. The most common form, especially for water-insoluble

drugs, is a powder suspension that is propelled into the mouth while the patient inhales. Propulsion is accomplished by use of pressurized gas or by any of a variety of mechanical means of entraining a fine powder into a gas or air stream. Common devices for this purpose include metered dose inhalers (MDIs), turbo inhalers, and dry powder inhalers. Each of these uses a different means of propulsion; however, a common characteristic is that once the therapeutic drug leaves the device it is, or becomes, a fine powder. In an MDI, the drug may be suspended or solubilized in a non-aqueous propellant, which is typically a chlorofluorocarbon or fluorinated hydrocarbon that is a liquid under pressure at room temperature. In turbo inhalers and dry powder inhalers, the drug is present in the form of a micronized powder.

The particle size distribution of the aerosolized drug compositions is very important to the therapeutic efficacy of the drug when delivered by inhalation. Studies of inhaled aerosols indicate that particles or droplets of greater than about 5 micrometers in mean aerodynamic diameter are effectively excluded from entry into the lungs and are captured in the nasal passages or throat and swallowed instead. Thus, the drug compounds delivered by these devices must be formulated in such a way that the mass median aerodynamic diameter (MMAD) is below 5 micrometers. In addition, even smaller particle sizes, on the order of 0.5 to 2.5 micrometers, are needed if the drug is to reach the alveolar sacs deep in the lungs. However, particles with acrodynamic diameter less than about 0.5 micrometers are likely to be exhaled before the drug is totally deposited on the lung surface.

Additional considerations for the use of powder-type drug delivery devices for inhalation include the limited amount of drug that can be contained in one or two puffs from the device and the need for the user to skillfully coordinate hand activation of the device with inhalation. This latter limitation is particularly important for those patients who are disabled, children, or elderly.

Nebulizers offer an alternative method of administering therapeutic agents to the lungs. These devices work by means of an air jet or an ultrasonic pulse that is applied to a solution producing a fine mist. Therapeutic agents dissolved or suspended in the solution can be incorporated into the mist. The patient then breathes the mist in and out over the course of several minutes of treatment, during which 1 to 3 mL of the drug

formulation is typically nebulized. Considerations of particle size mentioned above also apply to the droplet size of the mists. However, it is possible to rebreathe a portion of the mist during several minutes of treatment and increase the capture of the fine droplet fraction that can penetrate the lung most deeply. In addition, there is no need for coordination between hand action and breathing, making the nebulizer easier to use for patients. It may be possible, in some cases, to administer drugs not soluble in aqueous solution by nebulizing them in suspension. However, the droplet size of nebulized drug-containing suspensions cannot be smaller than that of the suspended particles. Therefore, the finer droplets produced from these systems would not contain any drug.

Thus, one limitation of nebulized formulations is that they are most suitable for those drug compounds that are sufficiently water soluble such that a therapeutic dose of the drug can be dissolved in from 1 to about 3 mL of aqueous solution. One way around this limitation is to formulate with polar organic solvents or aqueous solutions thereof. However, few organic solvents can be safely inhaled for prolonged periods. Most organic solvents that are currently approved for use in inhalation devices are propellants, such as chlorofluorocarbons (CFCs), which will soon be eliminated from manufacturing for environmental reasons, or the newer hydrofluorocarbons and low boiling hydrocarbons, all of which are expected to evaporate prior to penetrating the lungs. Such solvents can evaporate rapidly during nebulization and leave the drug behind in the device or in large particles that would be likely to be deposited in the mouth or throat rather than be carried to the lungs. Indeed, MDIs were developed to circumvent such problems.

Another way to overcome the solubility problem of the drug is to blend cosolvents such as ethanol, propylene glycol, or polyethylene glycol with water. However, there are limits to acceptable levels of these cosolvents in inhaled products. Typically, the cosolvents make up less than about 35% by weight of the nebulized composition, although it is the total dose of cosolvent as well as its concentration that determines these limits. The limits are set by the propensity of these solvents either to cause local irritation of lung tissue, to form hyperosmotic solutions which would draw fluid into the lungs, and/or to intoxicate the patient. In addition, most potential hydrophobic therapeutic agents are not sufficiently soluble in these cosolvent mixtures.

Thus, there is a need to develop improved systems that can solubilize water-

insoluble drugs for nebulization, and to minimize the levels of cosolvent necessary to accomplish this. The ideal system would have a cosolvent concentration below about 15% and in certain cases below about 5%. It would consist of non-toxic ingredients and be stable for long periods of storage at room temperature. When nebulized, it would produce droplets having an MMAD less than about 5 micrometers.

Droplet size considerations are not as critical for sinus or nasal administration, but it is still important to use safe, non-irritating ingredients. An additional consideration for both nasal and inhaled delivery is that some of the formulation will inevitably be tasted and swallowed. Therefore, acceptable taste and odor must be considered important parameters, especially for nebulized formulations where exposure is prolonged and where pediatric subjects form an important fraction of the probable patient population.

Anti-inflammatory corticosteroids, which are essentially water-insoluble drugs that act on inflammatory cells in the respiratory mucosa, are a type of therapeutic compounds in need of improved inhaled delivery. These steroids are useful in treating a variety of inflammatory diseases including asthma.

Asthma is a chronic obstructive disease of the lower airways. The major clinical and pathological features of asthma are (partially) reversible airflow limitations due to bronchial constriction, bronchial hyperreactivity to noxious stimuli such as allergens or cold air, and inflammation of the airways. Anti-inflammatory corticosteroids are useful in treating this last condition. They are the most effective group of therapeutic agents currently available for treating allergic asthma. The steroids suppress many inflammatory processes including inhibition of eosinophilia, epithelial shedding, and edema. The cellular basis of these actions is under active investigation.

Like other steroid hormone analogs, corticosteroids bind with high affinity to cytoplasmic receptor proteins in target cells. The receptor-steroid complexes migrate to the cell nucleus, where they interact with nuclear chromatin to control gene expression. The receptor binding is saturable and very small amounts of steroid suffice to elicit maximum cellular responses, including suppression of inflammation.

Anti-inflammatory steroids can act systemically as well as locally. Therefore, while systemic administration of anti-inflammatory steroids will diminish airway inflammation in asthmatics, it can also cause such adverse effects as general

immunosuppression and imbalances in mineral metabolism. The corticosteroids commonly used in asthma treatment have a high ratio of topical to systemic potency. That is, these corticosteroids are highly active when delivered directly to the site of inflammation but relatively inactive when passed through the systemic circulation. The portion of an inhaled dose which is swallowed and absorbed through the intestine or absorbed through the lung tissue into the circulation is subjected to metabolism by the liver and converted to less active compounds with short half-lives. These metabolites are quickly eliminated from the blood, reducing the incidence of systemic side effects.

Among the most commonly used steroids are aldosterone, beclomethasone, betamethasone, budesonide, cloprednol, cortisone, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluorometholone, flurandrenolone, fluticasone, halcinonide, hydrocortisone, icomethasone, meprednisone, methylprednisolone, mometasone, paramethasone, prednisolone, prednisone, tixocortol, triamcinolone, and others, and their respective pharmaceutically acceptable derivatives, such as beclomethasone diproprionate, dexamethasone 21-isonicotinate, fluticasone propionate, icomethasone enbutate, tixocortol 21-pivalate, triamcinolone acetonide, and others. Fortunately, some of these synthetic steroids have low potentials for systemic absorption because of their unique structures and metabolism.

Corticosteroids have usually been formulated as suspensions of micronized drug powder in chlorofluorocarbon vehicles or with chlorofluorocarbon-free propellants and delivered by metered dose inhaler. The choice of this type of carrier and apparatus was dictated by the fact that corticosteroids are very difficult to stabilize in aqueous media and frequently produce systems that exhibit crystal growth, precipitation, and/or aggregation of suspended or solubilized drug.

Corticosteroids have been formulated in different drug delivery systems for administration to the respiratory tract. U.S. Patent 5,292,499 relates to reverse micelle colloidal dispersions of hydrophilic pharmaceutically active compounds prepared with aerosol CFC propellant formulations useful for topical, endopulmonary, nasal, or inhalation administration.

U.S. Patent 5,208,226 describes the concept of using a novel combination

therapy, which has greater efficacy and duration of bronchodilator action than previously known combinations and that permits the establishment of a twice daily dosing regimen. The effective treatment consists of administration of a stimulant bronchodilator, salmeterol, and/or a physiologically acceptable salt thereof, combined with beclomethasone dipropionate in a form suitable for inhalation such as a metered dose inhaler with dry powder or chlorofluorocarbon-containing formulations.

U.S. Patent 5,474,759 discloses aerosol formulations that are substantially free of chlorofluorocarbons, and having particular utility in medicinal applications. The formulations contain a propellant (such as 1,1,1,2,3,3,3-heptafluoropropane), a medium-chain fatty acid propylene glycol diester, a medium-chain triglyceride, optionally a surfactant, and optionally auxiliary agents such as antioxidants, preservatives, buffers, sweeteners and taste masking agents. These formulations are used as carriers for the delivery of inhaled drugs such as albuterol, momestrasone, isoprenaline, disodium cromoglycate, pentamidine, ipratropium bromide, and salts and clathrates thereof.

Recently, several corticosteroid liposomal formulations have been under development. U.S. Patent 5,192,528 discloses the delivery of corticosteroids by inhalation for treating a variety of lung diseases. The carrier consists of an aqueous suspension of sized liposomes containing the drug. This liposome-entrapped drug form is then aerosolized, using a pneumatic nebulizer, to deliver the drug to the lung. Cholesterol and/or cholesterol sulfate can be incorporated into the system to delay the release of corticosteroid from the liposomes in the lung environment. These formulations have many advantages over microcrystalline formulations, including utilization of otherwise water-insoluble materials, sustained pulmonary release, and facilitated intracellular delivery. However, some general problems pertaining to liposomes regarding manufacturing processes, the use of synthetic phopsholipids (such as dilauroylphosphatidylcholine), and the distribution patterns of aerosolized liposomes in the lung may cause difficulties in the wide application of this type of aerosolized formulation.

There are as yet no marketed, commercial liposomal, micellar, or microemulsion formulations available for pulmonary delivery of corticosteroids.

SUMMARY OF THE INVENTION

The present invention provides compositions suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract and methods for the administration of said compositions.

In one embodiment, the corticosteroid composition contains from about 0.1 to about 20 percent by weight of a high-HLB surfactant component (HLB greater than about 10), for example, ethoxylated derivatives of Vitamin E such as tocopheryl polyethylene glycol 1000 succinate ("TPGS"). The HLB, or hydrophilic-lipophilic balance, is a measure on an arbitrary scale of the polarity of a surfactant or mixture of surfactants. For example, TPGS has an HLB between about 15 and 19. Generally, the corticosteroid composition contains the corticosteroid in an amount from about 5 μg/ml to about 1 mg/ml. The composition is aqueous-based, containing at least about 70 weight percent of an aqueous phase that can include buffering, tonicity, taste-masking, and preservation additives.

The corticosteroid composition can also contain one or more pharmaceutically acceptable cosolvents to aid in the processing of the composition and to increase the solubility of the corticosteroid. Such cosolvents include mono- and polyvalent alcohols, such as propylene glycol, ethanol, and polyethylene glycol. Optionally, the corticosteroid compositions also can contain such components as low-HLB surfactants (HLB below about 8) and/or oils. Low-HLB surfactants include phospholipids, medium-chain mono- and diglycerides, and mixtures thereof. Useful pharmaceutically acccptable oils include triglycerides and propylene glycol diesters of medium-chain fatty acids.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions containing corticosteroid compounds as active agents for the treatment of ailments and diseases of the respiratory tract, particularly the lungs, by way of nasal and pulmonary administration. The compositions can be formulated such that they contain the corticosteroid active agent(s) in a dissolved state. The formulations can be stored either in a concentrated form to be diluted at the time of use or a ready-for-use, diluted state. The present invention also sets forth methods for using the compositions for nasal or inhaled delivery.

The corticosteroid compositions of the present invention are preferably formulated with ethoxylated derivatives of vitamin E as the high-HLB surfactant component. An example of a preferred high-HLB surfactant from this class of surfactants is tocopheryl polyethylene glycol 1000 succinate ("TPGS"). TPGS is commercially available from Eastman Chemical Company as "Vitamin E TPGS", and has been used as a water-soluble Vitamin E supplement for oral ingestion. It is a waxy solid at room temperature and has melting point around 40°C. It has been found that the use of TPGS in corticosteroid compositions is particularly advantageous due to the ability of TPGS to solubilize corticosteroids and to form a stable micellar solution upon dilution in an aqueous phase, and also due to the neutral taste of TPGS when used in a corticosteroid composition that is administered either nasally or by inhalation. Consequently, an embodiment of the present invention that is particularly well suited for ease of manufacturing is one in which the corticosteroid compound is initially dissolved in TPGS to form a "concentrate" that is diluted with an aqueous phase to form the final corticosteroid composition. This composition is a micellar solution because the concentration of TPGS is far above the critical micellar concentration (CMC) of TPGS, which is about 0.02 wt. percent in water at 37°C. This embodiment is easy to manufacture, has a low level of excipients, and has a neutral taste for inhalation delivery.

Compositions designed for inhaled administration have a level of the high-HLB surfactant in the final, diluted corticosteroid composition from about 0.1 to about 20, preferably from about 0.25 to about 15, and more preferably from about 0.5 to about 5, percent by weight. Compositions designed for nasal administration have a level of the high-HLB surfactant in the final, diluted corticosteroid composition from about 1 to about 20, preferably from about 2.5 to about 15 and more preferably from about 5 to about 10, percent by weight.

The corticosteroids that are useful in the present invention generally include any steroid produced by the adrenocortex, including glucocorticoids and mineralocorticoids, and synthetic analogs and derivatives of naturally occurring corticosteroids having anti-inflammatory activity. Examples of corticosteroids that can be used in the compositions of the invention include aldosterone, beclomethasone, betamethasone, budesonide, cloprednol, cortisone, cortivazol, deoxycortone, desonide,

desoximetasone, dexamethasone, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluorometholone, flurandrenolone, fluticasone, halcinonide, hydrocortisone, icomethasone, meprednisone, methylprednisolone, paramethasone, prednisolone, prednisone, tixocortol, triamcinolone, and their respective pharmaceutically acceptable derivatives, such as beclomethasone diproprionate, dexamethasone 21-isonicotinate, fluticasone propionate, icomethasone enbutate, tixocortol 21-pivalate, and triamcinolone acetonide. Particularly preferred are compounds such as beclomethasone diproprionate, budesonide, flunisolide, fluticasone propionate, mometasone and triamcinolone acetonide.

The corticosteroid compound is present in the final, diluted corticosteroid composition designed for inhalation in an amount from about 5 μg/ml to about 5 mg/ml, preferably from about 10 μg/ml to about 1 mg/ml, and more preferably from about 20 μg/ml to about 500 μg/ml. For example, the preferred drug concentration is between about 20 and 100 μg/ml for beclomethasone dipropionate, between about 30 and 150 μg/ml for triamcinolone acetonide, and between about 50 and 200 μg/ml for budesonide, depending on the volume to be administered. By following the preferred methods of the present invention, relatively high solubilities of the corticosteroid can be achieved in an aqueous-based composition. The solubility of the corticosteroid can be greater than about 50, preferably greater than about 75, and more preferably greater than about 100, in some cases greater than about 150 or about 200, μg/ml.

Similarly, the corticosteroid compound is present in the final, diluted corticosteroid composition designed for nasal administration in an amount from about 50 μg/ml to about 10 mg/ml, preferably from about 100 μg/ml to about 2 mg/ml, and more preferably from about 300 μg/ml to about 1 mg/ml. For example, the preferred drug concentration is between about 200 and 900 μg/ml for beclomethasone dipropionate, between about 250 μg/ml and 1 mg/ml for triamcinolone acetonide, and between about 400 μg/ml and 1.6 mg/ml for budesonide, depending on the volume to be administered.

The corticosteroid composition can also contain various excipients that improve the storage stability of the composition, but which do not significantly affect the overall efficacy of the composition in its freshly prepared state. Such excipients include buffers, osmotic (tonicity-adjusting) agents, low toxicity antifoaming agents, and

preservatives.

Buffers are used in the present compositions to adjust the pH to a range of between about 4 and about 8, preferably between about 4.5 to about 7, and more preferably between about 5 and about 6.8. It has been found that for certain corticosteroids the pH can be lowered further to enhance the stability of the aqueous compositions. For example, in certain formulations, the preferred pH range is between about 3 and about 8, preferably between about 3.2 and about 6.5, and more preferably between about 3.5 and about 6. Budesonide is an example of a corticosteroid that has shown superior stability at these lower pH ranges. The buffer species may be any pharmaceutically approved buffer providing the aforementioned pH ranges, such as citrate, phosphate, malate, etc. A preferred buffer solution is citrate buffer with concentrations from about 0.0005 to about 0.05 M, preferably from about 0.001 to about 0.025 M, and more preferably from about 0.005 to about 0.02 M.

The osmotic agent can be used in the compositions to enhance the overall comfort to the patient upon delivery of the corticosteroid composition. It is preferred to adjust the osmolality of the composition to about 280-300 mOsm/kg. Such agents include any low molecular weight water-soluble species pharmaceutically approved for pulmonary and nasal delivery such as sodium chloride and glucose.

Preservatives can be used to inhibit microbial growth in the compositions. The amount of preservative is generally that which is necessary to prevent microbial growth in the composition for a storage period of at least six months. Examples of pharmaceutically acceptable preservatives include the parabens, benzalkonium chloride, thimerosal, chlorobutanol, phenylethyl alcohol, benzyl alcohol, and potassium sorbate.

Corticosteroid compositions that contain the high-HLB surfactant can be prepared as follows. TPGS will be used as the representative high-HLB surfactant for illustrative purposes. First, the TPGS may be heated to a temperature of at least about 40°C, preferably at least about 45°C, and generally about 45-60°C. The appropriate quantity of the corticosteroid compound is then dissolved in the molten TPGS at the same temperature, thus forming the concentrated corticosteroid composition. To achieve the final, diluted corticosteroid composition, the molten concentrated corticosteroid composition is slowly added under continuous stirring to an aqueous phase. The aqueous

phase is preferably water containing the additives necessary to adjust the pH and tonicity, and preservatives if the formulation is intended for multiple use. It is preferred that the aqueous phase be heated prior to the addition of the molten corticosteroid concentrate to aid in dispersion. Generally, the aqueous phase should be heated to about 55-85°C, more preferably from about 60-70°C.

It is preferred that the diluted corticosteroid composition be formulated by first dissolving the drug in the molten TPGS and then dispersing this concentrate in the aqueous phase. If the drug is added to a prediluted mixture of TPGS and aqueous phase, it may not be possible to achieve the final desired concentration of the drug in a dissolved state. To ensure that the drug is solubilized and stable in the diluted composition, it is preferred that the level of the drug in the concentrated composition be from about 1 to about 30 mg/ml, preferably from about 2 to about 20 mg/ml, and more preferably from about 2 to about 10 mg/ml prior to dilution. The level of water in the concentrated corticosteroid composition should be below 5% by weight, preferably below 2% by weight, and more preferably below 1% by weight, and in general, it is advantageous not to add any water to the concentrated corticosteroid composition.

The aqueous phase, which is composed of water and optionally buffering, tonicity, and/or preservation additives, is present in the diluted corticosteroid compositions containing TPGS in an amount of at least about 70, preferably at least about 80, more preferably at least 90, and even more preferably at least about 95, percent by weight. The various other additives, such as buffers, tonicity adjusting agents, and preservatives, are preferably blended into the compositions as part of the aqueous phase, and the use of the term "aqueous phase" is intended to include such components, if used.

It has been found that the inclusion of any one of a group of cosolvents in these TPGS corticosteroid compositions can aid in the processing of the compositions and in the solubilizing of the drug. Preferred cosolvents include mono- and polyvalent alcohols, such as propylene glycol, ethanol, glycerol, glycofurol (available as Tetraglycol from Sigma), ethoxydiglycol (available as Transcutol from Gattefossé), and polyethylene glycol (PEG) having an average molecular weight between about 200 and 4000, preferably between 200 and 1000, more preferably PEG 400, and combinations thereof. The cosolvents can be present individually in the final, diluted corticosteroid compositions in

concentrations from about 0.1 to about 20, preferably from about 0.25 to about 15, more preferably from about 0.5 to about 5, and even more preferably from about 0.5 to about 2.5, percent by weight. The total level of cosolvents combined in the final, diluted corticosteroid compositions is from about 0.1 to about 20, preferably from about 0.25 to about 15, more preferably from about 0.5 to about 10, and even more preferably from about 0.5 to about 5, percent by weight.

When preparing the corticosteroid compositions, the cosolvents can be added to the molten TPGS, to the TPGS/drug concentrate, or to the aqueous phase in which the TPGS/drug concentrate will be dispersed. Any way, stable diluted corticosteroid compositions can be produced with the drug in a dissolved state. If the cosolvents are blended with the molten TPGS prior to the addition of the drug, the temperature of this concentrate can then be reduced during the dissolution process. In general, the temperature of the TPGS/cosolvent mixture can be maintained below about 50°C, preferably below about 45°C, in order to dissolve the drug. In some cases, such as when a volatile cosolvent like ethanol is used, no heating is necessary to achieve dissolution. In addition, when the concentrated composition contains a cosolvent, it is not necessary to heat the aqueous phase used as the dilution medium to form the diluted corticosteroid composition.

Alternatively, the drug can be first dissolved in the cosolvent or blend of cosolvents at 20-50°C and then that solution is blended with the molten TPGS to form the concentrated corticosteroid composition.

Other preferred high-HLB surfactants that can be used in place of, or in admixture with, ethoxylated derivatives of vitamin E are polyethylene glycol fatty acid esters. The fatty acid moiety preferably has from about 8 to about 18 carbon atoms. A preferred polyethylene glycol fatty acid high-HLB surfactant product is "Solutol HS-15," available from BASF Fine Chemicals. Solutol HS-15 is a mixture of polyethyleneglycol 660 12-hydroxystearate (70%) and polyethylene glycol (30%). It is a white paste at room temperature that becomes liquid at about 30°C and has an HLB of about 15. Aqueous solutions of this surfactant, like those of TPGS, have a neutral taste. Similar preferred manufacturing processes and behavior regarding the dissolution of drugs, dilution methods, and the addition of cosolvents apply to Solutol HS-15 as those mentioned above

for TPGS.

The corticosteroid compositions can contain other high-HLB surfactants, such as ethoxylated hydrogenated castor oil (Cremophor RH40 and RH60, available from BASF), tyloxapol, sorbitan esters such as the Tween series (from ICI Surfactants) or the Montanox series (from Seppic), etc. The corticosteroid compositions preferably contain either, or both, of the ethoxylated derivatives of vitamin E or the polyethylene glycol fatty acid esters as all or part of the high-HLB surfactant component, and in general the sum of these two types of surfactants will account for at least 50%, preferably at least 75%, and more preferably at least 90% by wt. of the high-HLB surfactant component.

Optionally, low HLB surfactants, having an HLB value below about 8, can also be used in the present invention. Examples of such low HLB surfactants include phospholipids, such as phosphatidylethanolamine, phosphatidylcholine, and phosphatidylinositol; and medium-chain mono- and diglycerides, i.e., mono- and di-glycerides of C_8 to C_{12} fatty acids, and mixtures thereof. The low HLB surfactants can be used in general at levels from about 0.1 to about 3 percent by weight in the diluted composition.

Optionally, an oil can also be incorporated into the compositions. Examples of pharmaceutically acceptable oil compounds include triglycerides and propylene glycol diesters of C_8 to C_{12} fatty acids such as the Captex series available from Abitec. Oils can be used in general in levels from about 1 to about 30 percent by weight in the concentrated compositions and from about 0.1 to about 3 percent by weight in the diluted composition.

It is necessary to add the drug to the compositions containing high-HLB and low HLB surfactants, and/or cosolvents, and/or the oil compounds, to form the concentrated corticosteroid compostion prior to dilution with the aqueous phase.

The diluted corticosteroid compositions using high-HLB surfactants such as TPGS or Solutol HS-15 to solubilize the drug are believed to be micellar compositions. This belief is based on the fact that the critical micelle concentration for both TPGS and Solutol HS-15 is about 0.02% by weight at 37°C, which is below their concentration in the diluted corticosteroid compositions. If an oil component is present with or without a low HLB surfactant, an oil-in-water (o/w) microemulsion may be formed as the diluted corticosteroid composition.

The aforementioned diluted compositions can be administered to the body in the form of an aerosol. For administration to the respiratory tract, particularly the lungs, a nebulizer is used to produce appropriately sized droplets. Typically, the particle size of the droplet produced by a nebulizer for inhalation is in the range between about 0.5 to about 5 microns. If it is desired that the droplets reach the lower regions of the respiratory tract, - i.e., the alveoli and terminal bronchi, the preferred particle size range is between about 0.5 and about 2.5 microns. If it is desired that the droplets reach the upper respiratory tract, the preferred particle size range is between 2.5 microns and 5 microns. The nebulizer operates by directing pressurized air to fluidize the droplets of the diluted corticosteroid composition, which resultant aerosol is directed through a nozzle and subsequently through a baffle system that removes larger particles.

For the treatment of bronchial constriction, the diluted corticosteroid composition is prepared as described above. The corticosteroid for such treatment is preferably either beclomethasone dipropionate, betamethasone, budesonide, dexamethasone, flunisolide, fluticasone propionate, or triamcinolone acetonide, and is formulated in the concentrations set forth above. The daily dose of the corticosteroid is generally about 0.4 to 2 mg, depending on the drug and the disease, in accordance with the Physician's Desk Reference.

EXAMPLES

Various embodiments of the present invention are illustrated by the following examples, which should not be intended to limit the scope of the invention. The compositions of Examples 1, 2, 3, and 5 are suitable for inhalation via nebulization and the composition of Example 4 is suitable for nasal administration.

Example 1

The glucocorticoid beclomethasone dipropionate monohydrate was dissolved in premelted (50°C) TPGS at concentrations of 2.8 and 6.3 mg per gram. These concentrates were kept at 50°C during the entire solubilization process, which was about 15 min. While in this molten form, the concentrates were diluted at various volume ratios from 1:10 to 1:100 in various aqueous solutions such as hot (80°C) deionized water,

saline, malate buffer, citrate buffer, phosphate buffer, and 5% solutions of propylene glycol, PEG 200, or PEG 400 in any of the above. These diluted compositions were blended until any gel that may have formed when the TPGS concentrate came into contact with the aqueous phase was completely dispersed. Transparent, physically stable, diluted corticosteroid compositions without any precipitates were obtained containing about 28 to 420 μg/ml beclomethasone dipropionate. The diluted corticosteroid compositions were sterilized by passing them through a 0.22 micron sterile filter.

Example 2

Beclomethasone dipropionate monohydrate (4.2 mg) was dissolved in 995.8 mg of a binary liquid mixture of TPGS and ethanol (1:1 weight ratio) by briefly mixing at room temperature to form a concentrated corticosteroid composition. The concentrate was diluted 1:100 by volume in solutions of 5 wt.% PEG 400 in either deionized water, saline, or 20 mM malate, citrate, or phosphate buffer, by mixing for several minutes at room temperature. The resulting optically transparent, diluted corticosteroid compositions contained about 42 μg beclomethasone dipropionate per ml. The diluted corticosteroid compositions were sterilized by passing them through a 0.22 micron sterile filter.

The same concentrated corticosteroid composition was also diluted 1:50 by volume in the above-mentioned aqueous phases, and resulted in final formulations containing about 84 μg beclomethasone dipropionate per ml. These diluted formulations were physically and chemically stable for over a year at 5°C, 25°C/60% RH and 40°C/75% RH.

Example 3

Several corticosteroids – beclomethasone dipropionate, budesonide, and triamcinolone acetonide – were dissolved in binary mixtures of TPGS and a cosolvent selected from the group of ethanol, propylene glycol, PEG 200 and PEG 400. The weight ratio of TPGS to cosolvent was 1:1, and the resulting drug concentrations were between 1.4 and 4.0 mg/gram. It was necessary to heat the TPGS/propylene glycol and the TPGS/PEG mixtures to approximately 45°C for several minutes in order to dissolve the drugs, but dissolution could be achieved in the TPGS/ethanol mixture at room

temperature. The concentrates were diluted 1:50 by volume in an aqueous phase (5% wt. PEG 400 in deionized water) resulting in clear solutions containing from 28 μg to 80 μg per mL. The diluted corticosteroid compositions were sterilized by passing them through a 0.22 micron sterile filter.

Example 4

The composition of this example is suitable for nasal administration. Beclomethasone dipropionate monohydrate (2.8 mg) was dissolved in 997.2 mg of a 2:1 w/w mixture of PEG 200 and TPGS and then diluted (1:6.65 by volume) with deionized water. The final transparent solution contained 420 μg of beclomethasone dipropionate per mL of solution. The composition of the formulation is given below. The tonicity can be adjusted to about 300 mOsm/kg by the addition of glucose or sodium chloride.

Component	**Weight Percent** Concentrate Mixture	**Wt/Vol. Percent** After 1:6.65 Dilution
TPGS	33.24	5
PEG 200	66.48	10
Beclomethasone dipropionate	0.28	0.042
Deionized water	---	q.s.

The diluted corticosteroid compositions were sterilized by passing them through a 0.22 micron sterile filter.

Example 5

In order to assess the stability profiles of some of the corticosteroid compositions described in this invention, four formulations were made with the weight compositions given in the following table.

Component	Form. 1	Form. 2	Form. 3	Form. 4
Beclomethasone dipropionate	42 μg/g	42 μg/g	42 μg/g	42 μg/g
TPGS	1%	1%	0.5%	0.5%
Polyethylene glycol 400	.....	1%	5%	5%
Ethyl Alcohol (190 Proof)	.....	.....	0.5%	0.5%
Deionized Water	q.s.	q.s.	q.s.	.....
0.9% NaCl Solution	.....	.....	.....	q.s.

Formulations were stored in glass vials and blow-molded polyethylene ampules for the duration of the study. Various tests were used to assess the physical and chemical stability of the corticosteroid compositions given above.

Size and distribution of the dispersed material droplets in the aqueous solution of the above compositions were determined using a quasi-elastic light scattering technique. The experimental equipment consisted of a BI-200SM Goniometer and BI9000AT Digital Correlator from Brookhaven Instrument Corporation, and a Thorn EMI Electron tube for detection powered by a high voltage power supply, delivering 2000 volts, from Bertan Associates. A helium-neon laser from Spectra Physics was the light source, with a wavelength of 632.8 nm. The droplet size of the dispersed phase in all formulations before nebulization was about 10 nm, and remained constant for the duration of the study.

The MMAD and the corresponding geometric standard deviation (GSD) of the nebulized corticosteroid compositions were determined at time zero of the study. Saline was used as a reference. The experiments were done using a system consisting of a Proneb compressor and a Pari LC Plus Reusable Nebulizer (Pari Respiratory Equipment, Inc., Richmond, VA) equipped with an adapted mouthpiece, connected in series with an Andersen cascade impactor (Andersen Airsampler Inc., Atlanta, GA). A vacuum pump was connected to the outlet of the cascade impactor, and between them was an air flow controller which indicated a flow of about 28.3 L/min. A cascade impactor is a mechanical model of human lung, containing seven stages and a filter before the outlet, which represent increasing depths of penetration. The amount of excipients deposited on each plate was determined by the increase in the plate dry weight. Analogous results were obtained when determining the MMAD from the drug mass on each plate. This showed

that the drug travels in same manner as the excipients.

Formulation	MMAD (μm)	%GSD
1	2.939	2.81
2	2.294	2.46
3	2.795	2.48
4	2.165	2.42
Saline	2.216	2.16

Analysis for the corticosteroid content and degradation products in the above compositions was performed by HPLC. A Shimadzu LC 10A was used with a Supelcosil LC-318 column and UV/VIS detector monitoring absorbance at a wavelength of 254 nm. The isocratic method used 60% acetonitrile in deionized water at a flow rate of about 1.5 mL/min for 15 min. Visual examinations of the corticosteroid compositions under crossed polarized light films and by the naked eye were made on a weekly basis. These examinations were done in order to observe over time whether there was any phase separation, drug precipitate, turbidity or change in color. Results of the stability study at 40°C/75% RH after 12 weeks are shown below. From these data it can be concluded that the tested formulations are physically stable, meaning that there was no phase separation or precipitation of the drug under stressed conditions. No degradation of the corticosteroid was observed. Similar results were obtained from samples which were stored at 5°C and 25°C.

Formulation	Drug content, t = 0, μg/mL	Drug content, t = 12 wk μg/mL (%)	
		glass vials	LDPE ampules
1	43.09	45.08 (104.6)	45.49 (105.6)
2	42.55	43.80 (102.9)	44.32 (104.2)
3	41.96	42.91 (102.3)	43.06 (102.6)
4	41.31	41.55 (100.6)	41.26 (99.9)

Examples 6 through 8 describe additional compositions suitable for inhalation.

Example 6

These budesonide formulation compositions are suitable inhaled delivery compositions:

Component	Formulation 1	Formulation 2
Budesonide	100 µg/g	100 µg/g
TPGS	1 %	1 %
Propylene glycol	1.72 %	------
Polyethylene glycol 400	------	1 %
Sodium chloride	------	0.65 %
Citrate Buffer	97.27%	97.34%

Formulation 1 was prepared as the follows: a mixture of melted TPGS and propylene glycol in a weight ratio of 1:1.72 was first prepared at 45 to 50°C, then the resulting liquid concentrate was cooled to ambient temperature. Budesonide was then added and dissolved at ambient temperature. The concentrate was diluted at room temperature in 20 mM citrate buffer at pHs of 3.5, 4.0 and 4.5.

Formulation 2 was prepared similarly to formulation 1 with a mixture of melted TPGS and PEG 400 with a weight ratio of 1 to 1. The budesonide was dissolved by stirring at 35 to 40°C. The mixture was slightly warmed to reduce viscosity. Alternatively, budesonide will dissolve at room temperature by using appropriate mechanical mixing equipment. The resulting concentrate was then diluted at ambient temperature into solutions of 20 mM citrate buffer with the above pHs containing sodium chloride to adjust the tonicity.

After dilution all samples were sterilized by filtering them through a 0.2 µm Millipore sterile filters and placed in sterile low density polyethylene plastic vials. These formulations were kept in humidity and temperature controlled chambers at 5° C 25°C/60% RH and 40°C/75% RH (where RH is the relative humidity). The % recovery after 13.5 weeks from time zero is presented for each formulation and storage condition, in the following table:

pH	Formulation 1			Formulation 2		
	5°C	25°C	40°C	5°C	25°C	40°C
3.5	100.2	98.7	95.2	101.0	100.1	95.2
4.0	98.9	98.5	ND	99.1	100.0	94.8
4.5	99.8	100.0	ND	99.7	99.0	ND

ND designates "not determined," as these were below 95%.

Example 7

Budesonide compositions containing 0.5 mg/mL budesonide in the final concentrations were prepared and diluted in citrate buffer as described in example 6. The fomulations were:

Component	Formulation 1	Formulation 2
Budesonide	500 µg/g	500 µg/g
TPGS	3 %	3 %
Propylene glycol	1.5 %	------
Polyethylene glycol 400	------	3 %
Phenyl ethyl alcohol	0.25%	0.25%
Benzalkonium chloride	0.02%	0.02%
Sodium chloride	------	0.35 %
Citrate buffer	95.18%	93.33%

The potential of formulation 1 to deliver therapeutic doses of budesonide by inhalation was demonstrated in the following studies. The MMADs, GSDs, and the respirable fractions of the formulations were determined by nebulizing each for 15 minutes, using a Pari ProNeb compressor nebulizer, and entraining the nebulized mist through an Andersen cascade impactor (Andersen Air Samplers, Inc., Atlanta, GA) as described in Example 5. The Respirable Fraction is the ratio, given as a percent, of the drug deposited in stage 2 or lower in the cascade impactor to the total amount entering the device and provides an estimate of the fraction of the drug likely to reach the deeper areas of the lungs.

	Formulation 1 (Budesonide 500 µg/g - 3% TPGS)	Formulation 2 of Ex. 6 (Budesonide 100 µg/g -1% TPGS)
MMAD (µm)	2.15	2.26
GSD	2.75	2.76
Respirable Fraction (%)	63.3	61.8

Both the MMAD data and the respirable fraction data support the utility of these formulations for delivery of budesonide to the lung by way of inhalation. These formulations can also be used for nasal delivery using a spray device, preferably with the preservatives.

Example 8

The formulations described in Examples 6 and 7 were also prepared using lower buffer concentrations of 10 mM, 5 mM, and 1 mM with similar stability results. However, using buffer concentrations of 0.1 mM or less had an adverse effect on budesonide stability at accelerated temperatures (40°C).

Example 9

A composition containing fluticasone 17-propionate was prepared using 0.01 M citrate buffer, pH 5.0, as an aqueous phase. Fluticasone 17-propionate (27.5 mg) was dissolved in 9.9725 g of a 2:1 w/w mixture of TPGS and polyoxyethylene glycol 400 by stirring for 1 hour at 60°C. The hot concentrate was diluted (1:25 wt/wt) with 0.01 M citrate buffer, pH 5, containing 1.6% propylene glycol for tonicity adjustment, by mixing for 20 minutes at 60°C. The final transparent solution was sterilized by passing it through a 0.2 micron sterile filter and filled into sterile plastic low density polyethylene vials. The composition of the formulation is given in the following table.

Component	**Weight Percent** Concentrate mixture	**Wt/Wt Percent** After 1:25 Dilution
TPGS	66.487	2.6595
Polyethylene glycol 400	33.238	1.3295
Fluticasone 17-propionate	0.275	0.011
Propylene glycol	-	1.536
0.01 M citrate buffer, pH 5	-	94.464

This composition is suitable for delivery of fluticasone 17-propionate by oral inhalation using a nebulizer.

Example 10

The following fluticasone composition is suitable for nasal administration and contains benzalkonium chloride and disodium edetate as preservatives and sodium chloride as an osmolality adjuster.

The amount of 0.4 g of Fluticasone 17-propionate was added to 79.6 g of melted TPGS and a mixture was stirred at 60°C until homogeneous (approximately 1 hr). The concentrate was diluted (1:10 wt/wt) with an aqueous phase consisting of 0.01 M citrate buffer, sodium chloride, benzalkonium chloride and disodium edetate. The mixture was stirred at 60°C for 20 minutes (until homogeneous). The composition of the formulation is given in the following table.

Component	Weight Percent Concentrate mixture	Wt/Wt Percent After 1:10 Dilution
TPGS	99.5	9.950
Fluticasone 17-propionate	0.5	0.050
Sodium chloride	-	0.612
Benzalkonium chloride	-	0.020
Disodium edetate	-	0.050
0.01 M citrate buffer, pH 5	-	89.318

Example 11

This example contains two corticosteroid compositions that form oil-in-water microemulsions after dilution of the concentrate with an aqueous phase.

Fluticasone 17-propionate (38.5 mg) was dissolved in 9.9615 g of a mixture of TPGS-Captex 300 (9:1 by weight) by stirring for 1 hour at 60°C. The concentrate was diluted (1:35 wt/wt) with 0.01 M citrate buffer containing 1.8% propylene glycol as an osmolality adjuster by stirring for 10 minutes at 60°C. The composition of the final transparent formulation is given in the following table.

Component	Weight Percent Concentrate mixture	Wt/Wt Percent After 1:35 Dilution
TPGS	89.6535	2.5623
Captex 300	9.9615	0.2847
Fluticasone 17-propionate	0.385	0.011
Propylene glycol	-	1.7486
0.01 M citrate buffer, pH 5	-	95.3934

Captex 300 is a mixture of triglycerides of medium chain fatty acids. This composition is suitable for inhaled oral delivery of fluticasone 17-propionate using a nebulizer.

Example 12

This oil-in-water microemulsion composition contains a concentration of budesonide that is suitable for nasal administration. The following mixture was prepared and used as a nonaqueous phase:

	Weight percentage
TPGS	89.1
Captex 300	0.9
Capmul MCM	10

Budesonide (0.016 g) was dissolved in the above nonaqueous phase (1.984 g) by stirring at 55°C for 20 minutes. The prepared concentrate was then diluted (1:16) with 0.02 M citrate buffer, pH 5, containing sodium chloride and benzalkonium chloride. An optically transparent oil-in-water microemulsion was formed. The composition of the formulation is given in the following table. Capmul MCM is a mixture of mono- and di-glycerides of medium chain fatty acids.

Component	**Weight Percent** Concentrate mixture	**Wt/Wt Percent** After 1:16 Dilution
TPGS	88.3872	5.5242
Captex 300	9.9200	0.6200
Capmul MCM	0.8928	0.0558
Budesonide	0.8000	0.0500
Sodium chloride	-	0.6500
Benzalkonium chloride	-	0.0200
0.02 M citrate buffer, pH 5	-	93.0800

What is claimed is:

1. A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, consisting essentially of:

(a) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form,

(b) from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable, high-HLB surfactant component, wherein the HLB of the surfactants is greater than about 10, and

(c) at least about 70 weight percent aqueous phase.

2. The composition of claim 1 wherein the high-HLB surfactant component comprises at least 50% by weight of an ethoxylated derivative of vitamin E, a polyethylene glycol fatty acid ester, or a mixture thereof.

3. The composition of claim 2 wherein the high-HLB surfactant component comprises an ethoxylated derivative of vitamin E.

4. The composition of claim 2 wherein the high-HLB surfactant component comprises a polyethylene glycol fatty acid ester.

5. The composition of claim 2 wherein the corticosteroid comprises beclomethasone dipropionate.

6. The composition of claim 2 wherein the corticosteroid comprises budesonide.

7. The composition of claim 2 wherein the corticosteroid comprises triamcinolone acetonide.

8. The composition of claim 2 wherein the corticosteroid comprises fluticasone propionate.

9. The composition of claim 2 wherein the corticosteroid comprises flunisolide.

10. The composition of claim 2 wherein the high-HLB surfactant component comprises tocopheryl polyethylene glycol 1000 succinate.

11. The composition of claim 2 wherein the high-HLB surfactant component comprises polyethylene glycol hydroxystearate.

12. A composition suitable for administering a therapeutic dose of a corticosteroid to the respiratory tract, comprising:

(a) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form,

(b) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants is greater than about 10, and wherein the high-HLB surfactant component comprises an ethoxylated derivative of vitamin E, a polyethylene glycol fatty acid ester, or a mixture thereof; and

(c) at least about 70 weight percent aqueous phase.

13. The composition of claim 12 wherein the high-HLB surfactant component comprises an ethoxylated derivative of vitamin E.

14. The composition of claim 12 wherein the high-HLB surfactant component comprises a polyethylene glycol fatty acid ester.

15. The composition of claim 12 further comprising from about 0.1 to about 20 percent by weight of a pharmaceutically acceptable cosolvent comprising propylene glycol, polyethylene glycol having a molecular weight between about 200 and 4000, glycerol, ethoxydiglycol, glycofurol, and ethanol, or a combination thereof.

16. The composition of claim 12 further comprising from about 0.1 to about 3 percent by weight of a low HLB surfactant having an HLB below about 8.

17. The composition of claim 12 further comprising from about 0.1 to about 3 percent by weight of an oil.

18. A method for administering a therapeutic dosage of a corticosteroid to the respiratory tract, comprising:

(a) providing a corticosteroid composition comprising:

(1) from about 5 μg/ml to about 5 mg/ml of a corticosteroid in dissolved form,

(2) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants is greater than about 10, and wherein the high-HLB surfactant component comprises an ethoxylated derivative of vitamin E, a polyethylene glycol fatty acid ester, or a mixture thereof; and

(3) at least about 70 weight percent aqueous phase;

(b) aerosolizing the corticosteroid composition in a nebulizer; and

(c) administering a therapeutic effective dosage of the aerosol of the corticosteroid composition by inhalation.

19. The method of claim 18 wherein the corticosteroid composition consists essentially of said corticosteroid, said aqueous phase, and said high-HLB surfactant.

20. A method for administring a therapeutic dosage of a corticosteroid to the nasal passage, comprising:

(a) providing a corticosteroid composition comprising:

(1) from about 50 μg/ml to about 10 mg/ml of a corticosteroid in dissolved form,

(2) from about 0.1 to about 20 percent by weight of a high-HLB surfactant component wherein the HLB of the surfactants is greater than about 10, and wherein the high-HLB surfactant component comprises an ethoxylated derivative of vitamin E, a polyethylene glycol fatty acid ester, or a mixture thereof; and

(3) at least about 70 weight percent aqueous phase;

(b) administering a therapeutic effective dosage of the corticosteroid composition by nasal inhalation.

21. A method of preparing a diluted corticosteroid composition containing the corticosteroid in a relatively high, dissolved concentration, comprising:

(a) dissolving a corticosteroid compound into a molten pharmaceutically acceptable high-HLB surfactant component, wherein the HLB of the high-HLB surfactant component is greater than about 10;

(b) subsequently blending the molten high-HLB surfactant component containing the dissolved corticosteroid with an aqueous phase,

wherein the aqueous phase is present in an amount of at least about 70 weight percent, and the high-HLB surfactant component is present in an amount of from about 0.1 to about 20 weight percent of the diluted corticosteroid composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/14351

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 9/27, 31/56
US CL :424/450; 514/179, 180
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/450; 514/179, 180

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,478,860 A (WHEELER et al.) 26 December 1995, see entire document.	1-21
Y	US 4,567,161 A (POSANSKI et al.) 28 January 1986, see entire document.	1-21
Y	US 4,782,047 A (BENJAMIN et al.) 01 November 1988, see entire document.	1-21
Y	LY, J. et al. 'Evaluation and Application of Hydrophilic Tocopherol Polyethylene Glycol Derivatives as Enhancers of Drug Solubility.' In: College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, NY, Presentation ID: 3419, 05 November 1997, 1 page summary.	1-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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